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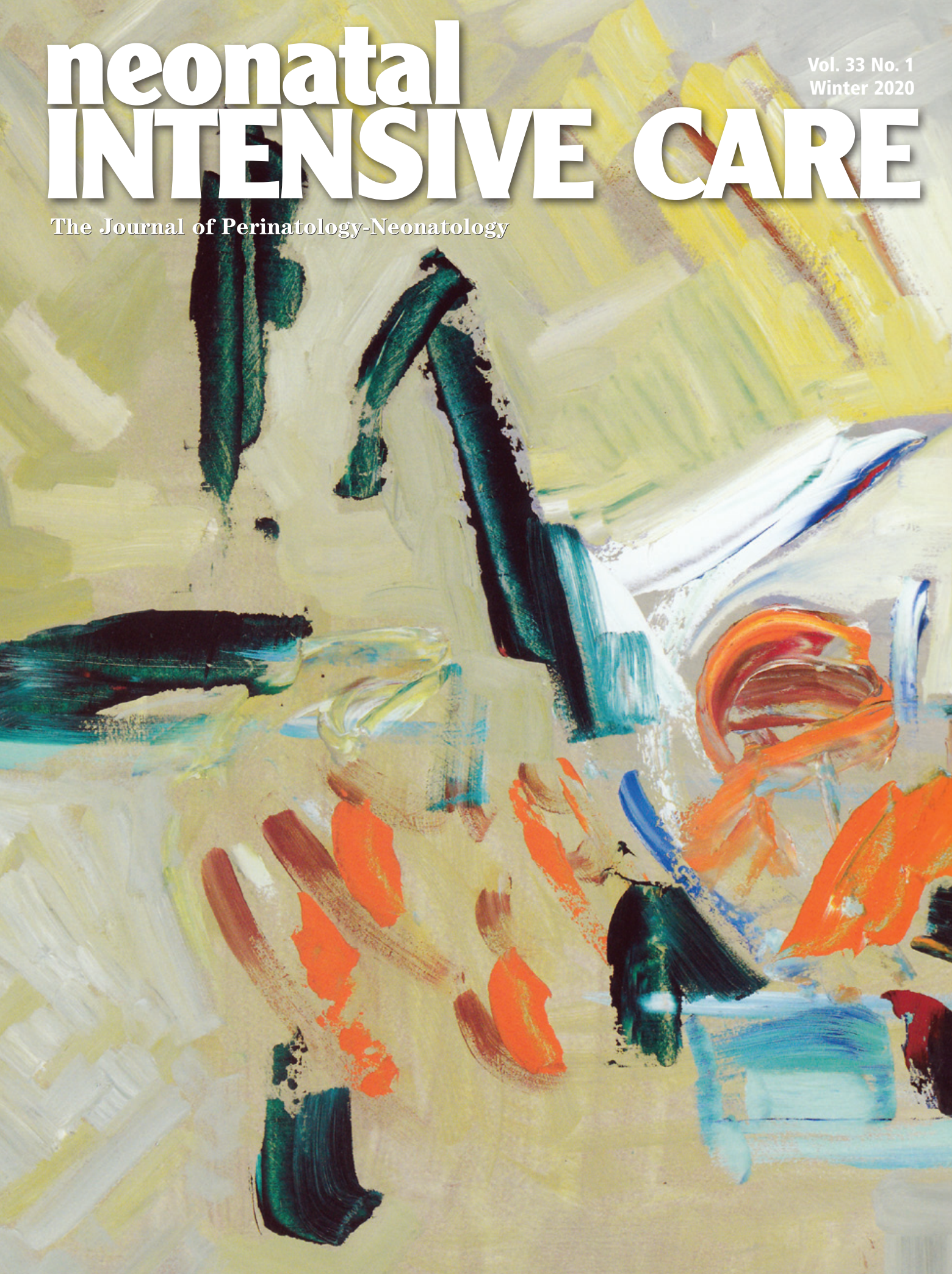

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Device With Improved Oxygen Saturation Gets FDA Clearance

Device maker Masimo announced that RD SET sensors with Masimo Measure-through Motion and Low Perfusion SET pulse oximetry have received FDA clearance for improved oxygen saturation (SpO2) accuracy specifications for neonatal patients (< 3 kg). The updated RD SET sensors' SpO2 accuracy specifications have improved significantly, from 3% to 1.5% ARMS (at 1 standard deviation), in conditions of motion and no motion, providing clinicians with even greater confidence when monitoring the oxygenation status of neonates. With this clearance, the improved performance specifications, which were incorporated into RD SET sensors for patients > 3 kg in 2018, are now available to all patient populations in the United States. Masimo's SET pulse oximetry has been shown in more than 100 independent and objective studies to outperform other pulse oximetry technologies—even before the revisions that achieved the improved accuracy specifications—providing clinicians with increased sensitivity and specificity to help them make critical patient care decisions. Crucially for newborn health, SET has been shown to help clinicians reduce severe retinopathy of prematurity in neonates3 and in multiple studies, including the largest critical congenital heart disease (CCHD) study to date, to improve CCHD screening in newborns. In addition to offering improved accuracy, RD SET sensors are designed to enhance patient comfort, optimize clinician workflows, and help hospitals meet green initiatives. The sensors are lightweight and have a flat, soft cable with smooth edges, so that they lie comfortably on a patient's hand or foot. In particular, RD SET NeoPt sensors with Velaid SofTouch use little to no adhesive, facilitating quick but gentle application and repositioning on the fragile skin of newborns and pre-term babies. RD SET sensors also feature an intuitive sensor-to-cable connection, while their lightweight design results in up to 84% less waste and their sleek, recyclable packaging reduces storage and shipping space. Joe Kiani, Founder and CEO of Masimo, said, "We're delighted to announce the latest result of our continued innovation in our foundational SET pulse oximetry. We have long been dedicated to helping improve the lives of neonatal, infant, and pediatric patients, and this clearance significantly furthers that mission. Thanks to the brilliance and dedication of our engineers and the continuing support of our customers, we've been able to once again raise the standard for pulse oximetry performance. Even though no one has been able to create pulse oximetry that outperforms SET, we have not allowed that to stop us from continuing our pursuit of perfecting pulse oximetry."

Spontaneous Breathing Trials Add Little Value: Study

Spontaneous breathing trials (SBTs) are increasingly being used to help determine readiness for extubation in mechanically ventilated extremely preterm neonates, but a new study suggests they provide little added value over clinical judgement alone and may be risky.

As currently performed, SBTs are "unwarranted in clinical practice because they may expose neonates to clinical instability without improving the ability to assess extubation readiness," Dr Guilherme Sant'Anna from Montreal Children's Hospital in Quebec and colleagues conclude. In a paper in JAMA Pediatrics, they report results of a diagnostic study of 259 neonates (birth weight <1250 g) from five neonatal intensive care units from the prospective Automated Prediction of Extubation Readiness (APEX) study. All of them required mechanical ventilation, were thought to be ready for extubation and underwent endotracheal continuous positive airway pressure (ET-CPAP) before extubation. The study team recorded cardiorespiratory signals

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during five minutes of ET-CPAP immediately before extubation and documented signs of clinical instability (apnea requiring stimulation, presence and cumulative durations of bradycardia and desaturation, and increased supplemental oxygen).

More than half of the babies (147 of 259; 57%) developed at least one of these clinical events during ET-CPAP; 10% suffered apneas, 19% bradycardias, 53% desaturations, and 41% had increased need for oxygen. Compared with babies who failed extubation (defined as reintubation within a week), babies with successful extubation (71%) had significantly fewer clinical events and shorter cumulative bradycardia and desaturation time and less increase in oxygen need. However, in an algorithm that included multiple clinical event combinations to define SBT success or failure, none had "sufficient accuracy to justify their routine use," the investigators report.

"Arguably," they write, documenting clinical events during ET-CPAP would be justifiable if it could accurately predict which babies would succeed or fail extubation. In their cohort, babies who failed extubation were significantly more likely to have clinical events compared to babies with successful extubation. However, there was "considerable" overlap between these two groups. "Consequently, when computing the diagnostic performance of all possible SBT definitions, none had an acceptable trade-off between sensitivity and specificity," they note. "In fact, given that nearly one-third of neonates who failed extubation had an uneventful ET-CPAP recording, they would have been automatically misclassified by any SBT definition." Their findings, they say, are in line with the only study to their knowledge to prospectively audit the consequences of incorporating routine SBTs into clinical practice. That study found that SBT-driven extubation did not improve extubation success rates compared with clinical judgment alone.

Nutritional Monitoring Found Lacking

Many neonatal intensive-care units (NICUs) in the US lack clinical-decision support (CDS) to calculate and monitor caloric intake for critically ill infants, according to a survey. "I hear about nutrition intake less often than I hear about fluid intake," Dr Gustave H. Falciglia of Northwestern University, Feinberg School of Medicine, and Ann and Robert H. Lurie Children's Hospital of Chicago, said. "Having dietitians on rounds has helped with this problem; however, we are performing these calculations manually or retyping data already within the electronic health record (EHR)." CDS provides real-time support to clinicians during order entry and has been shown to improve the quality and safety of nutrition of preterm infants in the NICU. Falciglia and colleagues surveyed clinicians at 34 NICUs participating in the Children's Hospital's Neonatal Consortium (CHNC) to determine the availability of CDS to calculate nutrition and fluids received in the prior 24 hours and to estimate projected nutrition and fluids that an infant should receive in the subsequent 24 hours. Only 32% of NICUs had CDS to determine enteral calories received and only 29% had CDS to determine parenteral calories received, whereas 82% had CDS to determine enteral and parenteral fluids received, the researchers report in the Journal of Perinatology. Similarly, only 24% of NICUs had CDS to project enteral fluids or calories, whereas 79% had CDS to project parenteral calories and 68% had CDS to project parenteral fluids. Even among NICUs with CDS, the majority did not have an automated CDS for nutrition received. Clinicians had to retype

data from the EHR into a calculator within the same EHR or into a calculator separate from the EHR. Only one surveyed NICU had an automated CDS that calculates both enteral and parenteral calories received.

Breathing Studied for Infants in Car Seats

When placed in car seats, babies who are only a week or two premature can have breathing problems similar to those faced by infants born much earlier, a new study suggests. The majority of preemies are born at 34 to 36 weeks' gestation, when they're considered late pre-term and lower risk for respiratory problems that are common among earlier arrivals with less-developed lungs, researchers note. The American Academy of Pediatrics recommends screening all preemies to ensure that they can sit in the semi-reclining position in car seats without breathing problems, but the study team notes that this test is often overlooked for late pre-term babies.

For the study, researchers examined car seat screening results for 918 late pre-term babies. Overall, 4.6% of these babies failed the test, meaning they could risk potentially fatal breathing difficulties by riding in a car seat. "Infants who spent time in both the neonatal intensive care unit (NICU) and the newborn nursery had the highest risk of failing, which is important for doctors to know when preparing these babies for discharge home," said senior study author Dr Natalie Davis of the University of Maryland School of Medicine, in Baltimore. "Even those who were thought to be the healthiest and did not require the NICU were at risk of unsafe breathing in the car seat," Davis said. "This emphasizes the fact that evaluating late preterm infants for fit and safe breathing in their car seat is important no matter how healthy they appear." In the study, 8.5% of babies who were in both the NICU and the newborn nursery before discharge failed the car seat screening tests. Among babies who failed these tests, 24% failed two or more assessments. Many of these babies had apnea or low oxygen levels, and 40% required oxygen to be discharged from the hospital.

All babies should be placed in car seats when they ride in a car. But the seats used by most newborns may not work for some late-term preemies because these babies are smaller, weigh less and have immature lungs, brains and hearts. Preemies may not breathe effectively for several weeks after birth. Among other problems, even late-term preemies may be too small to fit properly in car seats, and the straps may hit them in the wrong place on their body and make it harder to breathe, Davis said. Most car seats are designed for babies who weigh at least five pounds, and may not be safe for babies who weigh less, she added. Preemies also can have low muscle tone that increases the chance their head will flop from side to side in the car seat, or that they will sink or slouch down into an unsafe position that makes it harder for them to breathe, Davis noted. Parents of preemies should consult with a car seat specialist like a Certified Child Passenger Technician (CPST) to show them how to safely place their baby in the seat and use it in the car.

VERO Biotech Receives US FDA Approval

Biotech LLC, an Atlanta, Georgia-based biotechnology company focused on saving lives, alleviating suffering and improving the health economics of care, announced it has received US Food and Drug Administration approval of GENOSYL (nitric oxide) gas, for inhalation. GENOSYL is indicated to improve

oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents. GENOSYL is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood. VERO Biotech's GENOSYL Delivery System (DS) is a compact and user-friendly nitric oxide delivery system, that will not only enable hospitals to reduce logistical burden as compared to the cumbersome tank-based systems currently available, but could provide greater patient access to this potentially life-saving drug. "FDA approval is a major milestone for VERO Biotech and represents an alternative technology within the inhaled nitric oxide market," said Brent V Furse, President and Chief Executive Officer. "We look forward to making GENOSYL DS available to the critical care community and patients who may benefit from treatment. This is the first step towards VERO Biotech executing on its vision to bring innovative, patient-centric therapeutic solutions to market." VERO Biotech anticipates launching GENOSYL DS in US hospitals in early 2020.

Diabetes Risks Studied

Premature babies may be more likely to develop diabetes as children and young adults than full-term infants, a new study suggests. Compared to kids under 18 years old who were born full-term, those born before 37 weeks' gestation were 21% more likely to develop type 1 diabetes, and 26% more likely to develop type 2 diabetes in childhood. As adults, preemies were 24% more likely to develop type 1 diabetes and 49% more likely to develop type 2 diabetes by the time they were 43 years old. "Preterm birth interrupts normal development of multiple organ systems, including the pancreas where insulin-producing cells are formed, which may potentially contribute to later development of diabetes," said lead study author Dr Casey Crump of the Icahn School of Medicine at Mount Sinai in New York City. Some previous research suggests that preemies have an increased risk of developing insulin resistance. For the current study, researchers examined data on almost 4.2 million babies born in Sweden from 1973 to 2014. Median follow-up was 22 years. Overall, 0.7% of the study population went on to develop type 1 diabetes and just 0.1% developed type 2 diabetes, the researchers report in Diabetologia.

"Parents should know that most children who were born preterm will have good health in childhood and adulthood," Dr Crump said by email. "However, they also have modestly increased risks of diabetes that persist into adulthood." Overall, the risk tended to be higher for premature girls. Premature boys were about 20% more likely to develop type 1 diabetes during the study, while girls had about a 30% greater likelihood. With type 2 diabetes, preterm females were 60% more likely to develop the disease during childhood than full-term babies, while preterm males had no increased risk. For young adults in the study, women born preterm had a 75% increased risk of type 2 diabetes and men who were preterm had a 28% increased risk.

Many people in the study had siblings included in the analysis. Shared genetics and family circumstances appeared to explain some, but not all, of the increased risk of diabetes for preemies.

Study Examines SUIDs

Sudden unexpected infant deaths (SUIDs) in the first week of life differ from those occurring later, a retrospective study reveals. Studies usually group all SUID deaths together, but this research team "wanted to know whether there were statistically distinct groups within the SUID population based on age of death," Dr Tatiana Anderson of Seattle Children's Research Institute said. "We provide evidence that SUIDs that occur during the first week of life are a statistically separate entity, with different risk factors than deaths that occur outside the neonatal period," she said. "Some risk factors for post-perinatal SUID (death between 7-364 days) include young, single mothers and increasing live birth order, which are actually protective factors for sudden unexpected early neonatal death (SUEND; death between 0-6 days)," she noted. "SUEND deaths follow a distinct epidemiological pattern and should be considered independently in future SUID research, which may help uncover differing underlying physiological mechanisms or genetic causes," she added. The study included data on more than 41 million births from the US Centers for Disease Control and Prevention Birth Cohort Linked Birth/Infant Death Data Set (2003-2013), including more than 37,000 SUIDs. Following the definitions in the study, the SUEND group differed significantly from the post-perinatal SUID group in the distributions of assigned International Classification of Diseases, 10th Revision (ICD-10) code, live birth order, maternal marital status, age of mother, birth weight, and gestational length. More specifically, post-perinatal SUID rates were higher for children whose mothers were unmarried at their child's birth (adjusted odds ratio,1.19). By contrast, being unmarried decreased the risk of a SUEND (aOR, 0.72). Compared with mothers ages 25 to 29, younger mothers (ages 15-24) had statistically higher post-perinatal SUID rates but lower SUEND rates. By contrast, SUID and SUEND rates were both lower for mothers over 30 years old. Smoking in pregnancy was a significant risk factor for SUEND, but less so than for post-perinatal SUID (aORs, 1.44 versus 2.20, respectively). However, after adjustment, maternal smoking was not a significant risk for deaths that occurred in the first 48 hours (aOR, 0.89). Two covariates, marital status and the father's age, seemed to explain the change in significance. Importantly, after the first 48 hours, the risk related to maternal smoking sharply increased and peaked at approximately day 21(aOR, 2.34).

Treating HIV-Infected Infants Very Early Substantially Improves Health—Study

A small study of African infants infected with HIV found that giving them antiretroviral therapy within the first hours and days of birth helped preserve their immune systems, improving their chances of better long-term health, US researchers said. HIV infections in newborns pose a huge health burden in developing countries. One study estimated that 300 to 500 infants are infected every day in sub-Saharan Africa. "Without treatment, 50% of HIV-infected children progress to death within two years," study co-author Dr Roger Shapiro of the Harvard T.H. Chan School of Public Health said. The study, published in the journal Science Translational Medicine, builds on discoveries of infants whose HIV was thought to have been cured after receiving antiretroviral therapy (ART) within weeks of birth. The first such case involved a Mississippi infant born in 2010 who was treated within 30 hours of birth and was able to control her virus for several months after treatment was stopped. In the new study, a team of Harvard and MIT researchers tested this early treatment approach on a group of 40 HIV-infected infants in Botswana, where 24% of pregnant women are living with the virus that causes AIDS. The researchers reported results of the first 10 infants who were given ART within hours and days of birth, 10 infected infants who began treatment four months after birth

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and compared those with 54 infants without HIV. The earliest-treated infants showed a much smaller viral reservoir—the pool of virus that persists through life even during treatment—than the second infant group after 96 weeks, researchers reported. Babies in the earliest treatment group also had more robust immune systems than even the infants without HIV, researchers found. Current World Health Organization guidelines recommend infected newborns receive ART within weeks of birth to suppress the virus, which can otherwise quickly lead to rapid and fatal immune deficiency. Shapiro said the earlier treatment strategy is not a cure, but could be combined with other interventions as part of research toward an HIV cure. The research team said that some of the children may be enrolled in a trial testing the use of protective antibodies specifically engineered to neutralize HIV to see if the approach could help the infants control the disease without the need for lifelong treatment. That trial is set to start in 2020.

Immune Deficiency Foundation launches website supporting parents

The Immune Deficiency Foundation (IDF), a national organization for people with primary immunodeficiency (PI), announces the launch of a new website designed to support parents of babies diagnosed with severe combined immunodeficiency (SCID), a rare genetic condition that is fatal if not treated within the first year of life. The site, www.scidcompass.org, offers parents an in-depth explanation of SCID; detailed information on treatment options; advice on how to care for their child after treatment; and access to support systems where they can meet other families. The website is part of a broader project, the SCID Compass Program, funded by a two-year grant from the US Health Resources and Services Administration (HRSA). To develop and evaluate the family-centered website, IDF partnered with parents of children with SCID, grassroots support groups, and healthcare professionals with decades of experience working with families affected by SCID. Other partners included the Association of Public Health Laboratories (APHL), a professional association responsible for supporting newborn screening programs; the Genetic Alliance, a health advocacy organization; and RTI International, a non- profit research organization. IDF consulted with parents to build and review website content, employed the expertise of physicians in the writing and editing process, and utilized communication science teams to shape the website's core architecture. "Scidcompass.org is truly a product of teamwork and is presented in an accessible format that we hope parents will find clear, engaging and helpful as they navigate their journey living with SCID," said Heather Smith, Chairperson of the SCID Compass Steering Committee and President of SCID, Angels for Life, a non-profit support group for parents of children with SCID, which works closely with IDF. The launch of the website coincides with the one-year anniversary of all 50 states implementing screening for SCID in their newborn screening protocols. IDF, along with dedicated volunteers and partner organizations, lobbied lawmakers for 10 years to include SCID on the newborn screening panel and celebrated success in December 2018 when policy was approved requiring nationwide universal screening for SCID. "The website is a natural next step now that newborn screening for SCID is implemented in the US Now, more than ever, babies are being screened, diagnosed and treated for SCID. That means a probable increase in the number of SCID cases and a greater need for information," said John G. Boyle, President and CEO of the Immune Deficiency Foundation. "The website delivers a much-needed place for parents to not only educate themselves on this rare and life-threatening disorder, but also find a sense of comfort as they connect with others who have similar experiences."

VTE Treatment Studied

In children with acute venous thromboembolism (VTE), treatment with the direct oral anticoagulant rivaroxaban results in a similarly low recurrence risk and a lower thrombotic burden as parenteral anticoagulants, without increasing bleeding, researchers say. "As for many pediatric diseases, currently available medications for thrombosis have never been systematically studied and licensed for children," Dr Christopher Male of the University of Vienna said. "Current standard anticoagulants have a number of disadvantages, such as parenteral administration and need for frequent monitoring."

"The pivotal study had two key results," he said. "One, outcome frequencies such as recurrent thrombosis and bleeding, as well as relative treatment effects (rivaroxaban versus standard anticoagulants), were quite similar between adults and children, demonstrating that...the large body of data from adults can be used to inform the still-limited pediatric evidence." Secondly, he noted, "rivaroxaban in weight-adjusted fixed-dose regimens was shown to be at least as effective and safe in children as standard anticoagulants."

That said, he added, weight-relative doses and dosing frequency were different for younger children and infants, "showing that dosing cannot be simply down-scaled from adults but needs to be systematically studied and clinically validated." The open-label, randomized study involved 500 children up to age 17 with acute VTE in 107 pediatric hospitals in 28 countries. Participants who had started on heparin were assigned (2:1) to body weight-adjusted rivaroxaban (tablets or suspension) in a 20-mg equivalent dose or standard anticoagulants (heparin or switched to vitamin K antagonist). Randomization was stratified by age and VTE site. The 37 children under age two with catheter-related VTE were treated for one month; the other 463 participants were treated for three months.

Hiccups in Newborns Might Help Baby Brains Wire-Up

A long string of hiccups in a newborn can make parents uneasy. But researchers now say that those hiccups may aid in the baby's brain development. Each time a newborn hiccups, three brain waves are triggered, a large one and two smaller ones, a small new study finds. And those brain waves may help babies learn how to regulate their breathing, according to the report published in Clinical Neurophysiology."Hiccups may not be just a 'nuisance,'" said the study's lead author, Kimberley Whitehead, a research associate at University College of London. "They may play an important developmental function by strengthening the brain's sensory 'map' of the breathing muscles. Babies' brains appear to be registering the 'feel' of the hiccup, as they sense the movement of the diaphragm."

A typical bout of hiccups can last 8 minutes, Whitehead and her colleagues noted. While that may be worrisome to some parents, it's completely normal and quite possibly a necessary part of babies learning how to exert voluntary control over their breathing, Whitehead said. To learn more about the potential purpose of hiccups in babies, Whitehead and her colleagues studied 13 newborns in a British neonatal ward who were experiencing hiccups. The group of babies included some who were born full term and some who were pre-term. Electrodes

were placed on the babies' scalps to measure brain activity in a procedure known as electroencephalography (EEG). Movement sensors placed on the infants' bellies provided information on when the baby was hiccupping. Recordings of the two types of measurements were temporally linked so researchers could determine if there could be a connection between the hiccups and certain types of brain activity. After looking at the two sets of recordings, Whitehead and her colleagues determined that each hiccup was associated with a complex pattern of brain activity. The researchers found that contractions of the diaphragm muscle from a hiccup were associated with three brain waves, the third of which looked similar to what is evoked when a baby hears a noise. They suspect that the newborn's brain could be linking the 'hic' sound of the hiccup with the feel of the diaphragm muscle during contraction. The first two waves may be associated with the brain wiring up circuits that control breathing, Whitehead suggested.

Genome Sequencing in Newborns Raises Ethical Issues

Screening newborns for health risks using genomic sequencing can raise ethical and equity questions, the authors of a new paper warn. Testing newborns for a handful of specific childhood conditions is already commonplace in the US "Newborn screening is often done without parental permission and has been justified on the grounds that the direct benefits to the child greatly outweigh the harms," said Dr Lainie Friedman Ross of the MacLean Center for Clinical Medical Ethics at the University of Chicago in Illinois, who co-authored the case study. However, these tests are done to identify conditions that can be diagnosed and treated early. Sequencing all or large parts of a baby's genome at birth could reveal genetic variations that increase risk for conditions that occur in childhood or not until adulthood. The conditions could be benign or ultimately be untreatable later, Ross said. "To justify screening all infants in mandatory programs, we need to ensure that the benefits greatly outweigh the harms, and we cannot say this is the case for many of the variants we will identify by sequencing," she said. In 2014, the National Institutes of Health funded four projects to study the benefits and risks of genomic sequencing for newborns. One of them, the BabySeq Project, explored the medical, behavioral and economic impacts of sequencing. As part of that clinical trial, half of the babies were randomly assigned to receive sequencing along with usual care. And parental consent included an agreement to receive any results related to childhood-onset conditions. During the study, however, a sequencing report showed that one baby carried a BRCA2 mutation, which can be associated with an increased risk of breast cancer. Although the family didn't have a history of breast cancer, the research team felt moral distress about not being able to disclose the information because it wasn't related to a childhood disease. The BabySeq researchers approached their institutional review board and asked for permission to disclose it and then told the baby's parents. Ultimately, the study protocol was modified to require all participating families to agree to receive information about adult-onset conditions, too. When Ross and co-author Dr. Ellen Wright Clayton of the Vanderbilt University Medical Center in Nashville, Tennessee, read about the dilemma and the protocol change, they thought the decisions were morally problematic. "If we do research on our children, we need to consider what rights they have to privacy (particularly about information that will not be relevant until they are adults) and what harms as well as what benefits may accrue from seeking out this information years or decades before it is necessary," Ross said. Generally, professionals in the pediatric, genetics and ethics communities

agree that children shouldn't be tested for adult-onset-only conditions, Ross and Clayton write. One argument against testing for adult risk emphasizes the child's right to an "open future" and to make the choice as an adult about what they want to know. The BabySeq researchers asserted that if the mother's life might be saved by learning she is at increased risk for cancer, then the whole family, including the infant, benefits from having her alive, and that may outweigh other harms. But Ross and Clayton reject the argument for a "family benefit."

RAIT Gets Rated

Receipt of radioactive-iodine treatment (RAIT) after thyroidectomy for thyroid cancer does not appear to be associated with adverse pregnancy outcomes when conception occurs six months or more after treatment, researchers from South Korea report. "Women are concerned about the risks associated with pregnancy after radioactive iodine treatment," Dr Hye Ok Kim from Health Insurance Review and Assessment (HIRA) Service and Ewha Womans University, in Seoul, said "Therefore, accurate information about the recommended interval between radioactive iodine treatment and conception is critical for childbearing-age women and their treating physicians." RAIT is commonly associated with oligomenorrhea and is a risk factor for congenital malformations. The American Thyroid Association and the European Association of Nuclear Medicine Therapy Committee recommend avoiding pregnancy for at least six months after RAIT, albeit based on relatively low quality of supporting evidence. Kim's team used data from South Korea's HIRA database to investigate whether RAIT was associated with an increase in adverse pregnancy outcomes among more than 10,000 women who became pregnant after thyroidectomy for thyroid cancer; 55% had surgery alone, while the rest had surgery plus RAIT. Conception rates in the RAIT group were significantly lower than in the surgery-only group in both the 0-to-5- and 6-to-11-month intervals after treatment but did not differ between the groups in the 12-to-23 months after treatment. Overall, there were no significant differences between the surgery-only and surgery-plus-RAIT groups in rates of abortion (spontaneous and induced), preterm deliveries or congenital malformations, the researchers report in JAMA Internal Medicine. Among women who received RAIT, congenital malformation rates were higher, though not significantly so, for those whose interval between treatment and conception was 0 to 5 months (13.3%) versus 6 to 11 months (7.9%), 12 to 23 months (8.3%), or 24 months or more (9.6%). After adjusting for age at conception and cumulative radioactive iodine dose, the odds of congenital malformation were 74% higher (P=0.04) for early conception (0 to 5 months after RAIT) versus late conception (12 to 23 months after RAIT). The cumulative dose of radioactive iodine, however, was not associated with the risk of congenital malformations. The odds of abortion were also significantly higher (OR, 4.08) among women who received RAIT less than six months before conception versus those who conceived later.

Breast Milk Bank Launched

The five mothers sat in a bright blue room in Kenya's largest maternity hospital waiting to pump breast milk—but not for their own newborns. At Kenya's first breast milk bank, the women were waiting to help infants whose mothers couldn't feed them by donating some of their own milk. Antibody-rich breast milk helps premature and sick babies recover faster. Although infants benefit most from their own mother's milk, milk from donors—if safely collected and pasteurized—is a good alternative, the American Academy of Paediatrics says. Six months ago, the Ministry of Health and the African Population and Health Research Centre set up Kenya's first breast milk bank at Nairobi's Pumwani Maternity Hospital. The project is a pilot to see if similar banks can be set up elsewhere in the country, said Elizabeth Kimani-Murage of the research centre. So far, 75 infants have received nutrient-rich breast milk from about 400 donors. Their mothers were either absent, ill, unable to lactate, or with substance-abuse problems, said Faith Njeru, the unit's head nurse. First, Njeru and her team had to make people comfortable with the idea of milk donation. There are milk banks in South Africa, Mozambique, and Cape Verde but many Kenyans had not heard of the idea. Evelyn Wawira thought the idea was strange when she first heard of it during her pregnancy with her second son. "Here, breastfeeding somebody else's baby is not heard of," she said. "You have your reservations—is it safe? Is it possible?"

But then Wawira realized she could help save a life by pumping milk for the bank while also feeding her newborn son. "They're just babies!" she said over the whirr of the unit's electrical breast pumps. "It's not their fault they don't have milk ... As long as the baby can have it and it will save his life, why not?"

Moderate Weight Gain May Be Healthiest in Twin Pregnancies

Pregnant women may be "eating for two"—or more—but when it comes to twin pregnancies, gaining too much weight may be as bad as gaining too little, a US study suggests. There isn't a lot of evidence for an ideal amount of weight gain in a twin pregnancy, the study team writes in Obstetrics & Gynecology. But in a large analysis of twin pregnancies, they found that both very high and very low weight gain was associated with more preterm births and infant death. Gaining too little weight was also linked with having babies that were small for their gestational age, and gaining too much was tied to overly-large babies and cesarean deliveries, researchers reported. "Twin pregnancies have high rates of complications, so it is important to identify factors that we can modify during pregnancy to lessen these risks," said Lisa Bodnar of the University of Pittsburgh in Pennsylvania, who led the study. During the past 40 years, the number of twins born in the US has doubled, Bodnar noted, and twins account for about 3% of births but more than 20% of preterm births. Women carrying twins are also more likely to experience diabetes, preeclampsia and cesarean deliveries. The National Academy of Medicine recommends that women who are normal-weight or underweight gain 17-25 kilograms (37-55 pounds) during a twin pregnancy, and that overweight women gain no more than 11-19 kg (24-42 lbs). "We've known for a long time that twin pregnancies carry a much higher risk of poor outcomes, and weight gain is a very common conversation for a pregnant woman and her doctor to have," Bodnar said. "However, the lack of evidence on what that optimal range is left women and their doctors to make educated guesses or not to discuss weight gain at all." Bodnar and colleagues analyzed data from nearly 55,000 twin births in Pennsylvania from 2003 to 2013. Small-for-gestational-age and preterm birth before 32 weeks were most common among women who were underweight before pregnancy, they found. And large-for-gestational-age birth and cesarean delivery were more common with higher pre-pregnancy body mass index. For normal-weight women, pregnancy weight-gain also appeared to influence risk. For example, compared with a weight gain of 20 kg, or about 44 lbs, a gain of 27 kg, or 60 lbs, was associated with 2.2 fewer cases of small-for-gestational-age but 2.9 more cases of large-for-gestational-age and 3.7 more

cases of cesarean delivery. Over the study period, weight gains in nearly one in three women fell outside the National Academy of Medicine guidelines, the authors note.

Newly Diagnosed Hodgkin Lymphoma Can Be Safely Managed During Pregnancy

Hodgkin lymphoma diagnosed during pregnancy can be safely managed without interruption of pregnancy in most cases, according to new findings. "Maternal outcome is not worse when compared to nonpregnant patients," Dr Frederick Amant of University Hospitals Leuven, KU Leuven, in Belgium, said. "This is important since gestational changes result in chemodilution and hence the hypothesis that chemo may be less effective. This is not the case, so that is an argument not to interrupt pregnancy but preserve the pregnancy and treat the mother." Previous studies have documented reassuring birth outcomes in mothers with Hodgkin lymphoma, and increased awareness of the feasibility of antenatal chemotherapy has led to more pregnant women receiving anticancer drugs. For their study, Amant and his colleagues used data from the International Network on Cancer, Infertility and Pregnancy (INCIP) obtained from 17 academic centers in 11 countries. They evaluated the management and obstetric outcomes of 134 pregnant women diagnosed with Hodgkin lymphoma during pregnancy, compared with 211 nonpregnant women with Hodgkin lymphoma matched for stage and prognostic score at diagnosis. During pregnancy, 56 women (42%) received no therapy, 72 women (54%) received chemotherapy and six women (4%) received radiation therapy. The most common chemotherapy regimen, administered to 66 women, was ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) at standard doses. Most pregnancies (120, 90%) resulted in a live birth. There were two stillbirths and two miscarriages, and 10 women (7%) diagnosed in the first half of pregnancy opted for termination of pregnancy. Significantly more women receiving antenatal therapy had preterm complications, mainly contractions (12% vs. 7%) and preterm rupture of membranes (5% vs. 0). The incidence of neonates who were small for gestational age did not differ significantly between chemotherapy-exposed and non-exposed neonates. Four of 123 children (3%) had a major congenital anomaly at birth, and four children had minor physical abnormalities. About a third of children were admitted to the neonatal intensive-care unit, mainly due to prematurity.

Most Preterm Babies Are Healthy in Adulthood

More than half of premature infants grow up to be healthy adults without chronic medical issues, a new study suggests. Researchers followed 2.56 million babies born in Sweden between 1973 and 1977 until they were 30 years old on average, including about 149,000 premature infants. Each decade, preemies' odds of survival to adulthood improved, from about 91% of preterm infants born in the 1970s to about 96% of those born in the 1990s. About 55% of preterm infants in the study had no serious chronic physical or mental health issues by early adulthood, compared 63% of full-term babies, researchers reported. "Our findings reflect the apparent resilience of preterm birth survivors in maintaining good health," said Dr Casey Crump, lead author of the study and a researcher at the Icahn School of Medicine at Mount Sinai in New York City. "Despite increased risks of several chronic disorders, the majority can still have good overall health in adulthood," Crump said by email. In the current study, researchers focused on chronic health issues that typically develop in adolescence and young adulthood like asthma, high blood pressure, diabetes and mental health issues,

as well as health problems that can surface later like chronic lung, kidney, and liver diseases. Just 22% of extremely preterm babies—those born at 22 to 27 weeks gestation—were alive without any serious chronic health problems by the end of the study. But rates of this outcome got steadily better with longer gestations. About 49% of very preterm babies—born at 28 to 33 weeks—and 58% of late preterm infants—born at 34 to 36 weeks—were alive and generally healthy by early adulthood, the study found. These outcomes were similar for men and women.

Ranibizumab, Aflibercept Appear in Breast Milk After Intravitreal Injection

The anti-vascular endothelial growth factor (VEGF) agents ranibizumab and aflibercept are excreted in breast milk following intravitreal injection, researchers from Canada report. "Prior to this study, the minimal scientific literature in this area suggested that anti-VEGF drugs were not excreted into the breast milk, although this was based on studies involving only one specific drug, bevacizumab," said Dr Rajeev H. Muni of Saint Michael's Hospital and the University of Toronto. Muni's team sought to measure the levels of anti-VEGF agents and of VEGF in the breast milk of three lactating women who received intravitreal injections. In the first patient, who discontinued breastfeeding before intravitreal ranibizumab injection, ranibizumab was detected on day 3 after injection with generally increasing levels over time. VEGF concentrations in breast milk decreased from 22.8 ng/mL at baseline to 12.3 ng/mL on day 1 and to 4.9 ng/mL on day 28.

The second patient received an intravitreal ranibizumab injection four weeks before baseline, continued receiving ranibizumab therapy, and breastfed regularly throughout treatment. Breast milk ranibizumab levels remained below detectable levels throughout all study time points, and VEGF concentrations remained mostly unchanged.

This is "likely because the drug in the breast milk was constantly excreted and ingested by the infant and never accumulated sufficiently to be above the lower limit of quantitation," the researchers say. The third patient, who decided not to breastfeed, had detectable aflibercept in breast milk on day 4, and breast-milk VEGF concentrations declined from 10.6 ng/mL at baseline to 4.9 ng/mL on day 1, the researchers report. VEGF concentrations in breast milk decrease in the first 30 days after birth, so some of the reduction in VEGF concentrations observed in these patients could be related to reduced production, the researchers suggest.

Reducing Obese Moms' Sitting Time Lowers Fat Mass in Newborns

Improving diet, increasing physical activity, and reducing sedentary time among obese pregnant women seems to have a knock-on effect on their babies, who were born with lower fat mass than the offspring of women in control groups, a new analysis of the Vitamin D and Lifestyle Intervention study for gestational diabetes prevention (DALI) trial has shown. Mireille van Poppel, PhD, from the Institute of Sport Science, University of Graz, Austria, presented the results at the European Association for the Study of Diabetes (EASD) 2019 Annual Meeting. Of interest, "It was the sedentary behavior that seems to be responsible for the change in neonatal body composition [according to leptin and skinfold measurements], not the reduction in gestational weight as many people might have thought," remarked van Poppel. She stressed that this is one of the first reports of a link between the two and the finding about sedentary time provides an important message for public health. "Sitting less, getting out of a chair, and pottering around the house can be effective in terms of health benefits, which might be easier to do, especially in pregnancy, than having to be more active by going to a fitness center or gym," she said.

VENTILATION ROUNDTABLE

Getinge

What ventilation products does your company offer?
Servo-u and Servo-i Universal ventilators, Servo-n Neonatal ventilator. All provide Personalized Ventilation with NAVA and Edi monitoring.

What are the new features?
We continuously provide upgrades and updates to our ventilators, and therefore make sure that Servo ventilators can be kept up-to-date and support users changing needs over the lifetime of the ventilator. With the launch of our 2.1 Software we have new features but would like to highlight our New Servo Compass software which visually depicts low tidal volumes and peak pressures so adjustments can be made quickly to keep patients on target. In addition we also launched High-Flow Therapy which delivers a gas flow volume aligned with inspiratory flow rate to help reduce your patient's work of breathing.

Tell us about your company's current or recent R&D efforts.
Our latest software update is due to Getinge's investment in innovations in new therapies functionality and usability.

Discuss the training and support services you offer.
We offer product training to clinicians and staff. For the Biomed side, Getinge certified technical training is also available. Getinge Care Service Plans and technical support is available 24 hours/7 day a week.

Where are your products used? (ie, hospital, home, etc.)
We provide ventilators for Neonatal Intensive Care Units and Intensive Care Units.

What developments do you foresee for ventilation products and applications?
We believe strongly in Personalized Ventilation, to make sure the ventilation therapy is tailored to the individual patient. To achieve this we develop our NAVA technology, tools that facilitate for clinicians to tailor ventilator settings, and put significant resources in Human Factors engineering to make sure the full potential of our ventilators is easily understood by user´s and that they can use it with confidence.

The Benefits of Swaddle Bathing in Family-Centered Care

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Rachel Frazetti, BSN, RNC-NIC, who works as a Core Charge nurse at Anne Arundel Medical Center's Level III NICU located in Annapolis, Maryland. She is actively involved in the unit's Developmental Committee, Quality Committee, hospital based Informatics Committee, and recently won an award for Exemplary Professional Practice.

Neonatal Intensive Care: What prompted you to implement a study on swaddle bathing?
Rachel Frazetti: There were a couple of factors prompting this study. First being our unit is very conscience of developmental care and our bathing method before implementing swaddle bathing was not developmental friendly. Secondly, bathing was not prioritized; I found that infants were not being bathed regularly. Research has shown that swaddle bathing supports family-centered care, decreases physiologic and motor stress, conserves energy, improves state control, enhances ability to feed after bath, decreases temperature loss, causes less crying, and facilitates social interaction.

NIC: What was your previous method for bathing?
RF: Before we implemented swaddle bathing in the Turtle Tub we would either sponge bathe or use an emesis basin for submerged bathing.

NIC: How did infants respond to the previous bathing method?
RF: Infants were stressed and upset with the sponge bathing and using an emesis basin was very cumbersome and only could be done if the infant was small enough to fit.

NIC: What were the results of the swaddle bathing study?
RF: With the initiation of swaddled immersion bathing, the NIPS scores were found to be significantly lower in comparison to sponge bathing or basin bathing; pre-intervention NIPS average of 4.33 to post intervention and the use of the swaddle bathing the overall average was 0.73. There also was a decrease in the number of infants who were hypothermic post swaddled bathing; 26.7% pre-intervention and 5.1% post intervention.

NIC: Could you please describe the NIPS tool used to quantify infant stress? What is the test and what behaviors are included in the scoring?
RF: NIPS is used in children less than one year of age, typically for pain but we felt it applied to stress as well. This scale (0 to 7) uses body language: facial expression (relaxed or grimacing), cry (quiet, whimper, or vigorous cry), breathing pattern, arm and leg movement (extended, tense, or relaxed), and state of arousal (quiet, sleeping, or fussy). We found with sponge bathing infants were grimacing, crying, and quite fussy. Our average NIPS before we started swaddle bathing was 4.33 the average score and with implementing swaddle bathing it dropped to 0.73. Most infants were completely relaxed with swaddle bathing, some were actually sleeping during the bath.

NIC: Could you please describe in more detail how the nurses were educated to swaddle bathe? What training materials did you use? How much time did it require? Who did the education?
RF: Every nurse and tech on the unit were required to watch a video on how to swaddle bathe and then took a quiz. We used the information provided with the Turtle Tubs to use to educate. I recruited a few nurses to be Swaddle Bath Champions along with our educator and myself. The four of us performed demonstrations to staff of how to swaddle bathe and promoted swaddle bathing on the unit.

NIC: Do families bathe infants on your unit? If so, how has the response been? If not, what prevents families from participating in bathing?
RF: We attempt to involved parents in as much care of their infant as possible, which includes bathing. The parents have loved swaddle bathing in the Turtle Tub! I have had many families purchase the tub online to use after discharge.

NIC: The amount of time for bathing was not included in your study; however, do you perceive that there has been a change in the amount of time required for bathing since converting to swaddle bathing?
RF: While the time to bathe was not measured during the study I do think the time is the same or shorter than before. Part of implementing swaddle bathing was creating bath carts that have all of the needed supplies to bathe. This makes it easier and faster for the nurses to get everything they need for the bath. Another huge perk is that the families are now more comfortable bathing so the task can be performed independently by them with the nurse in the room.

NIC: Did you encounter resistance in changing to swaddle bathing? If so, how did you overcome the resistance? If not, what helped smooth the transition?
RF: As with any change, there was a little resistance to the new process. It helped to create the bath carts which made the process easier for the nurses. Additionally, I created cute

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

laminated signs in the shape of a turtle that said "I like to be bathed in the Turtle Tub". These were placed on the isolette/crib of infants that qualified to be bathed in the Turtle Tub. This was a great visual reminder for the nurse and also spurred the family to ask questions and be involved in bathing.

NIC: What bathtub did you use for the study? How do you think the tub contributed to the success of the study?
RF: We used the Turtle Tub and found it be to be perfect for swaddle bathing. The tub allows for immersion and cradles the infant well. Another perk is the thermometer at the bottom so nurses and parents know the water temperature is correct. Our unit loves the tubs so much that our Mother-Baby unit decided to purchase them as well to replace the tubs they were using for immersion bathing.

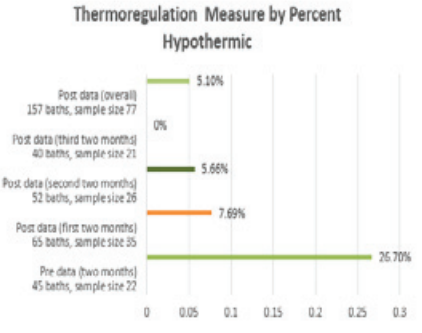
Swaddle Bathing in the NICU to Improve Thermoregulation and Decrease Stress

Anne Arundel Medical Center

Rachel Crosby, BSN, RNC-NIC, Kristen Hammerer, BSN, RNC-NIC, Tara Stoudt, MS, RNC-NIC, Cathaleen Ley, Ph.D, RN

Background/Introduction

Bathing is one of the most common routine nursing procedures performed on newborns, historically done without regard to the infant's stress response or developmental care. Within the NICU, it is of the upmost importance to attempt to limit and control these stressors. Research has shown that swaddled immersion bathing supports family-centered care, decreases stress, conserves energy, improves state control, enhances the ability to feed after bathing, decreases temperature loss, causes less crying, and facilitates social interaction. Pre-intervention, the NICU bathed infants by either using an emesis basin for immersion bathing or by administering a sponge bath. Both of these bathing methods can be stressful for NICU infants. Our average NIPS was 4.33 and 26.7% of the infants were hypothermic (less than 97.7 axillary) post bath.

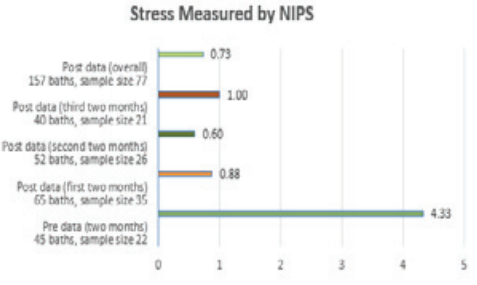


Purpose/Objectives

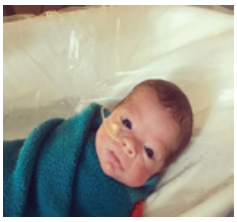
The purpose was to implement swaddled immersion bathing in the NICU to decrease stress and increase thermoregulation.

Methods

We focused our study on infants who were either born or adjusted to 30 weeks; 157 baths performed, sample size 77. We excluded infants who had IV access, required respiratory support higher than 3L of high flow nasal cannula, had an umbilical cord or had recently been circumcised. The effectiveness was measured by obtaining pre and post bath axillary temperatures to track thermoregulation and a NIPS score to measure the infants' stress response. Steps included: collecting data for two months before implementation using the data collection sheet; educating NICU staff (video, quiz, and sign off on the new bathing method); implementation of swaddled immersion bathing using the Turtle Tub; and post-implementation data collection.



Results



With the initiation of swaddled immersion bathing, the NIPS scores were found to be significantly lower in comparison to sponge bathing or basin bathing; pre-intervention NIPS average of 4.33 to post overall average of 0.73. There also was a decrease in the number of infants who were hypothermic post swaddled bathing; 26.7% pre-intervention and 5.1% post.

Conclusions and Implications/Lessons Learned

The goal was achieved as the NICU had a significantly lower percentage of hypothermic infants after the bath and our NIPS score decreased significantly.

We recommend adopting swaddled immersion bathing in NICUs and on Mother Baby units, as well as teaching families to swaddle bathe at home.

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Rachel Crosby, BSN, RNC-NIC; rcrosby@aahs.org

Pulmonary Hypoplasia in a Premature Twin

Ruchi Babriwala, MD and Shabih Manzar, MD

Summary

We present a case of a premature infant with pulmonary hypoplasia (PH) diagnosed clinically and radiologically. The cause for PH was prolonged premature rupture of membrane. Infant developed bilateral pneumothorax secondary to need for high pressure ventilation. Infant responded to inhaled nitric oxide and high frequency ventilation. Follow up chest X-ray at two weeks of life showed postnatal lung growth.

Case

A preterm twin 1 male infant was delivered to a 33-year-old gravida 4, para 1,1,2,3, at 29-6/7 weeks of gestation. Pregnancy was complicated by monochorionic diamniotic twin gestation, preeclampsia and history of previable premature rupture of membrane at 19 weeks. Mom received antenatal steroids at 23 weeks and then rescue dose at 27 weeks. All maternal prenatal lab including RPR, HIV, hepatitis B, chlamydia and gonorrhea were negative. Blood group was A positive and coombs negative.

Infant was delivered by cesarean section. At delivery, he was noted to have weak respiratory effort. He was placed on pre-heated warmer, dried and stimulated. Positive pressure ventilation (PPV) was provided using T-piece resuscitator (Neopuff) with positive end expiratory pressure (PEEP) of +6 at 60% FiO_2. He started crying. He was then placed on nasal cannula and transported to neonatal intensive care unit (NICU) for further management. Apgar scores were 5 and 7 at 1 and 5 minutes respectively.

On examination in the NICU, weight was 1.23 kg (2 lb 11.4 oz) – 32%, length of 39 cm (1' 3.35") – 50% and head circumference of 25 cm (9.84") – 5%. Admission vital signs were: temperature 98 °F (36.7 °C), heart rate 181, respiration 78, blood pressure 61/48, oxygen saturation (SpO_2) 88%. Head was normocephalic and anterior fontanelle was flat. Pupils were equal, round, and reactive to light. Cardiovascular exam showed regular rhythm and no murmur. Chest exam revealed tachypnea and sub costal retractions. Abdomen was soft with normal premature genitalia. His tone was normal for age and skin was warm with no lesions.

Ruchi Babriwala, MD is a Pediatric Resident, Department of Pediatrics. Shabih Manzar, MD is an Attending Neonatologist, Division of Neonatology, Louisiana State University of Health Sciences (LSUHSC), Shreveport, LA. Correspondence: Shabih Manzar, MD, 1501 Kings Highway, Shreveport, LA 71130, Telephone: 318-626-4374, Fax: 318-698-4305, Email: smanza@lsuhsc.edu.

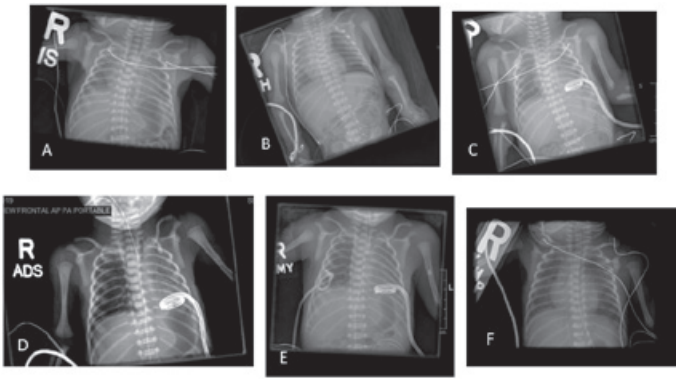

Figure 1. Serial Chest X-ray (CXR) showing the sequence of events
A: CXR taken soon after birth
B: CXR showing left pneumothorax
C: CXR after left chest tube insertion
D: CXR showing right pneumothorax
E: CXR after right chest tube insertion
F. CXR after extubation

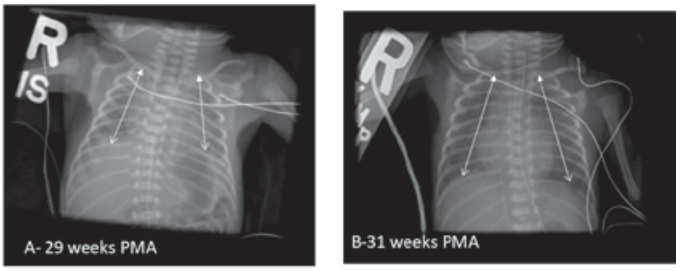

Figure 2. Chest X-ray comparing lung expansion
A: At birth
B: At 14 days of life
PMA – post menstrual age
White arrows showing the expansion of lungs

Hospital Course

Infant continued to have low oxygen saturation. He was intubated and a dose of surfactant was given. The blood gas continued to show respiratory acidosis. He was placed on high frequency oscillator ventilator (HFOV) with no improvement. An urgent chest X-ray (CXR) was obtained that showed left-sided pneumothorax. A chest tube was inserted and infant had some improvement, but continued to have frequent desaturations. The ventilatory settings were increased and a repeat CXR was obtained that revealed right-sided pneumothorax. Another chest tube was placed that resulted in SpO_2 improvement. Inhaled nitric oxide (iNO) was started at 20 parts per million

(ppm). Infant's condition started to improve reflected by further improvement in the oxygen saturations and blood gases. Table depicts the serial blood gas analysis results while serial CXR are displayed in Figure 1.

At day 4 of life, left chest tube was removed and subsequently on day 9 right chest tube was removed. Infant continued to wean down on FiO_2 to 23% and iNO was discontinued on day 9 of life. Infant was successfully extubated to bubble CPAP on day 11of life. The follow up chest X-ray at two weeks of life showed postnatal lung growth (Figure 2).

Discussion

The incidence of pulmonary hypoplasia (PH) in neonates with history of early gestational premature rupture of membranes (PROM) ranges from 9% to 28%.[1] The hallmark of PH is respiratory distress at birth, as noted in the case. The history of PROM at 19 weeks of gestation was the clue to the diagnosis of PH. PROM results in loss of amniotic fluid that is essential for fetal lung growth and development.[2]

The diagnosis of PH could be made in pathology lab by measuring the lung to body weight ratio and looking at radial alveolar count.[3-4] PH is diagnosed radiologically with the observation of a small chest size with upward shift in the diaphragm.[5] The clinical diagnosis of PH is made by signs of respiratory distress coupled with increase need for high ventilator pressures and response to inhaled nitric oxide (iNO). As pathologic diagnosis is made at autopsy, clinicians rely on radiology and physical findings for a clinical diagnosis. The sequence of events, as depicted in Figure 1, supports the clinical diagnosis of PH in the case presented.

The severity of PH observed in the case relates to PROM. The longer is the rupture of membrane (ROM) the more likely would be the development of PH. Winn et al[6] explained this relationship in their study. They looked at the latency period, defined as the duration between rupture of membranes and delivery, and amniotic fluid index (AFI) and combining both to predict the probability of PH. The longer the latency and lower the AFI, the more likely is the development of PH.

The treatment of PH consists of antepartum and postpartum interventions. Amnioinfusion has been tried but with controversial results.[7] Similarly, sealant use to patch the leak has not been effective.[8] Postpartum management includes gentle ventilation with HFOV and iNO. The American Academy of Pediatrics (AAP), Committee of the Fetus and Newborn, states that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure.[9] However, a recent survey by Manja et al[10] showed that the use of iNO among the neonatal practitioners was 78% despite the AAP recommendations. Similarly, the benefit of iNO in PH is debatable. A case series of six preterm infant showed benefit while the other case series of 185 preterm infants showed no benefit.[11,12]

Conclusion

Premature rupture of membrane early in gestation is a high risk factor for development of PH in neonates. Pneumothorax is a potential complication of PH secondary to need for high pressure ventilation. Gentle ventilation and iNO remains the mainstay of the treatment. Further studies looking into stem cell research to promote lung development in these cases are needed.

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A Newborn with Hypertension: Connecting the Dots

Shabih Manzar, MD

Summary

A 12-day-old premature male infant presented to the university hospital with elevated blood pressures. A thorough work up revealed the diagnosis.

Case

The infant was transfer from outside hospital (OSH) at 12 days of life. He was born at 30-2/7 weeks gestation to a 19-year-old gravida 2, para 0-0-1-0 mother. The pregnancy was complicated by a Di-Di twin pregnancy with a demise of the fetal twin in the second trimester, an abnormal antenatal screen (Nuchal Translucency > 12mm) and premature rupture of membrane. All prenatal labs including RPR, HIV, and Hepatitis B were negative. It was a vaginal delivery with no complications. Apgar scores were 6 and 8 at 1 and 5 minutes respectively. The infant received 30 seconds of delayed cord clamping and was immediately placed on nasal CPAP and transferred to the NICU. The infant's birth weight was 1710 grams.

Infant initial course at OSH was unremarkable except for high blood pressures for which he was transferred to the university hospital for further work up and treatment. On admission, vital signs were: temperature 97.9 °F (36.6 °C), heart rate 187 beats per minute, respiratory rate 47 per minute, blood pressure (BP) 83/61 mm of Hg (follow up was 120/65), and oxygen saturations 94%. Physical examination was normal. Pediatric nephrologist was consulted and a thorough work up was undertaken. Infant was started on antihypertensive therapy. Figure 1 depicts the BP and heart rate over time.

Discussion

Infant was found to have a left dysplastic kidney. Pediatric urologist was consulted and in view of the normal right kidney function, a conservative approach was followed. Figure 2 presents the common renal causes leading to hypertension. Figure 3 showed the Doppler results of renal ultrasound, no sonographic criteria met for renal artery stenosis. The right kidney measured 3.1 x 1.6 x 2.0 cm with the left kidney measuring 2.8 x 1.7 x 1.7 cm. There was mild prominence of the central renal pelvis of the right kidney without overt caliectasis or hydronephrosis. The renal cortex was of normal echogenicity

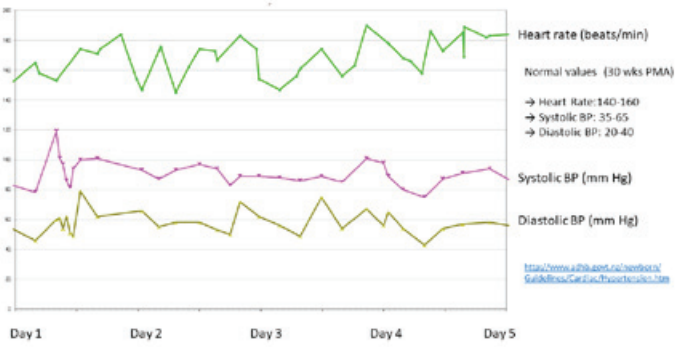

Figure 1

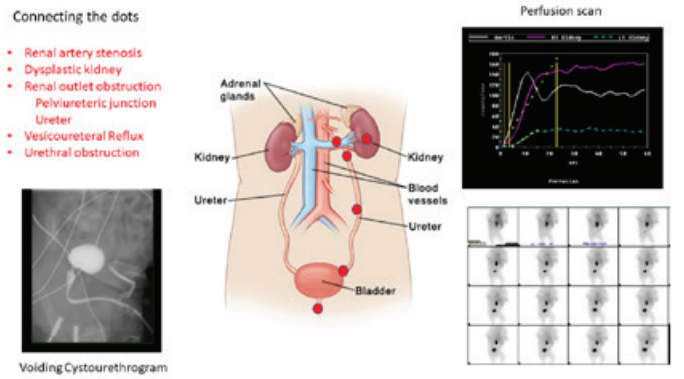

Figure 2

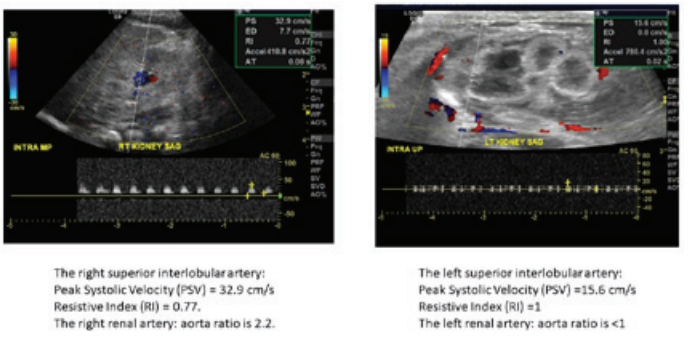

Figure 3

on the right with normal corticomedullary differentiation. No definite mass lesion was seen. On the left, there was markedly increased echogenicity of the renal cortex with preservation of the medullary portion of the kidney. Prominent hydronephrosis

Shabih Manzar is an Attending Neonatologist, Department of Pediatrics, College of Medicine, Louisiana State University of Health Sciences, 1501 Kings Highway, Shreveport, LA 71130. Address correspondence to Shabih Manzar, MD, 1501 Kings Highway, Shreveport, LA 71130, Telephone: 318-626-4374 Fax: 318-698-4305, Email: smanza@lsuhsc.edu.

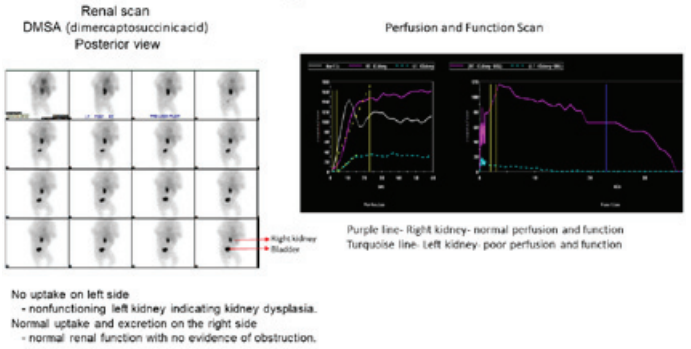

Figure 4

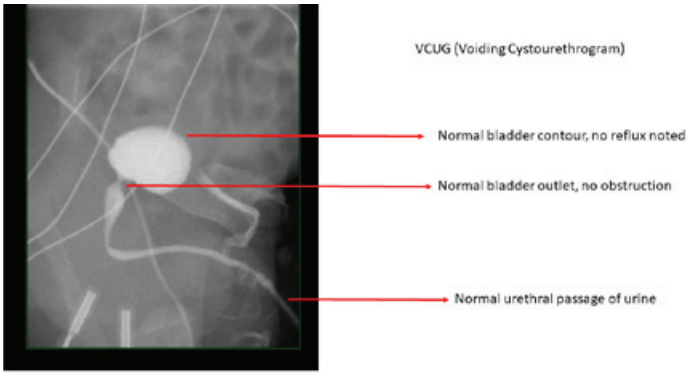

Figure 5

was seen. There appeared to be decreased vascularity within the left kidney. DMSA (dimercaptosuccinic acid) renal scan showed poor uptake and perfusion of left kidney (Figure 4) while VCUG (Voiding Cystourethrogram) showed no reflux.

Hypertension is an uncommon problem seen in NICU. Any infant with persistent elevated BP should be evaluated and treated promptly.

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The Role of Iron in Infant Nutrition

Sandra Sundquist Beauman, MSN, RNC-NIC

Introduction

Nutritional needs of a very premature infant can be complicated. There are nutrients, many of them referred to as micronutrients that are passed to the developing fetus and difficult to duplicate accurately when providing nutrition to the very premature infant. Iron is a nutrient understood to be important throughout the lifetime, particularly as it relates to erythropoiesis, the development of red blood cells.

Iron deficiency is the single most common nutritional deficiency worldwide and premature infants are at highest risk for iron deficiency for a variety of reasons (Schneider, Garcia-Rodenas, 2017). It has been estimated that as many as 600 million children worldwide are anemic and it is assumed that at least half of these cases are due to iron deficiency (WHO at https://www.who.int/elena/titles/iron_infants/en/). This is more common in children during periods of rapid growth as iron is needed for cell growth in general, but particularly for blood cells. This iron deficient anemia can lead to childhood morbidity and impaired cognitive development.

The iron needs of premature infants are known to be high for several reasons. They have fewer iron stores since the majority of iron is transferred during the last trimester of pregnancy. Iron needs are high because they have rapid physical growth between 28 and 38 weeks gestation and often have iron losses due to phlebotomy performed in the NICU (Moreno-Fernandez, Ochoa, Latunde-Dada, Diaz-Castro, 2019). Infants of diabetic mothers or small for gestational age also have iron deficiency whether born at term or preterm (MacQueen, Baer, Christensen, 2017). Therefore, compensating for low iron stores and iron losses is important. More studies are needed to demonstrate the best practices around iron supplementation, including how best to evaluate infants for iron needs. The purpose of this paper is to discuss the available evidence, recommendations and current practices regarding iron supplementation in very premature infants.

Why is iron important?

Iron is necessary in the development of every cell in the body. It is essential for energy metabolism and cell differentiation (Moreno-Fernandez, Ochoa, Latunde-Dada, Diaz-Castro, 2019). Rodent studies have shown that the higher the rate of metabolism, the more iron is necessary (Zhu, Wang, Wu, Wang, 2019). The neonatal brain consumes about 60% of the total oxygen required by the body showing that there is a high rate of metabolism, therefore, indicating an increased need for iron for adequate brain development. Iron is also necessary for nerve myelination and the function of neurotransmitters (Schneider, Garcia-Rodenas, 2017). Iron deficiency during infancy is associated with poor neurodevelopmental outcome including hearing loss (Grantham-McGregor, Ani, 2001; Angulo-Kinzler, Peirano, Lin, Garrido, Lozoff, 2002; Amin, Orlando, Wang, 2010). When iron deficiency is accompanied by hypoxic-ischemic encephalopathy, there is more risk to the developing brain (Zhu, Wang, Wu, Wang, 2019). Iron deficiency may also affect other organs including skeletal muscle, heart and the gastrointestinal tract (Moreno-Fernandez, Ochoa, Latunde-Dada, Diaz-Castro, 2019).

While there are many concerns about iron deficiency in infancy and childhood, iron overload can lead to serious consequences as well particularly for premature infants. Iron is believed to lead to oxidative stress and free oxygen radical injury due to an immature antioxidant capacity (Moreno-Fernandez, Ochoa, Latunde-Dada, Diaz-Castro, 2019). Iron overload is associated with an increased risk of bronchopulmonary dysplasia and retinopathy of prematurity. Therefore, appropriate levels of iron are important.

Evaluating for iron sufficiency

While many recommendations exist for iron dosing, needs of individual infants vary. Evaluating iron levels may be helpful, particularly in the premature infant when iron needs are high and iron supplementation is ongoing. It is known that iron is prioritized for erythropoiesis at the expense of brain development when iron levels are low (Zamora, Guiang, Widness, Georgieff, 2016). This demonstrates the need to identify low iron levels early and supplement sufficiently.

Iron levels may be measured by various laboratory indicators. The most commonly used, specific to iron is the serum ferritin level. Ferritin acts as an iron carrier in plasma and stores iron intracellularly and is, therefore, an indirect measure of iron levels (German, Vu, Juul, 2018) A low ferritin level, defined as less than or equal to 75 ng/mL (Amin, Bansai, Varley, Wang, Amin, 2019) indicates low iron stores. The limitation of this test though, is that the ferritin level is falsely elevated in the

Sandra Sundquist Beauman has been a neonatal nurse for her entire career, spanning over 30 years. She is currently a research nurse coordinator at the University of New Mexico and an independent consultant with Medela LLC. She also provides neonatal consultation and continuing education though CNS Consulting.

Table 1

Committee on Nutrition, American Academy of Pediatrics	All preterm infants: Start by 1 month; continue to 12 months 2 mg/kg/day	Baker RD, Greer FR. Committee on Nutrition, American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics. 2010;126(5):1040-50.
Nutrition Committee, Canadian Pediatric Society	Start at 6 to 8 weeks. Birth weight ≥1000 grams; 2-3 mg/kg/day. Birth weight <1000 grams; 3-4 mg/kg/day.	Canadian Medical Association. Nutrient needs and feeding of premature infants. Nutrition committee, Canadian paediatric society. CMAJ. 1995 Jun 1;152(11):1765-85. Unger SL, Fenton TR, Jetty R, Critch JN, O'connor DL. Iron requirements in the first 2 years of life. Paediatrics & Child Health. 2019 Dec 9;24(8):555-.
Committee on Nutrition of the Preterm Infant, European Society of Paediatric Gastroenterology and Nutrition	Preterm infants < 2000 gms: Start no later than 8 weeks; continue to 12 months 2-3 mg/kg/day for the first year of life	Domellof, M, Braegger C, Campoy C, et al. Iron requirements of infants and toddlers. J Pediatr Gastroenterol Nutr 2014;58(1):119-29.

presence of infection or inflammation making it less helpful in identifying iron overload (German, Vu, Juul, 2018). Another test used is Zinc protoporphyrin/heme (ZnPP/H) which is an indirect measurement of iron in the red blood cell (German, Vu, Juul, 2018). German, Vu, Juul (2018) compared Ferritin levels and ZnPP/H levels. They found that ZnPP/H were less impacted by inflammation than Ferritin levels. Hemoglobin and hematocrit may also be measured but a drop in these values may or may not be related to iron deficiency and once these levels fall, iron deficiency has already occurred.

There is some data about use of the reticulocyte hemoglobin (RET-He) as a measure of available iron. In a prospective nested study, ferritin and RET-He levels at 35-36 weeks gestation were compared in infants born at 24 to 32 weeks (Amin, Bansal, Varley, Wang, Amin, 2019). Those infants who had any indication of infection or inflammation such as culture-proven sepsis, C-reactive protein >5 mg/L within 10 days of iron status assessment were excluded. The ferritin level and RET-He were found to correlate as an indicator of iron status in this population. Advantages of using the RET-He value for iron measurement include that it is available in many settings as part of a complete blood count and does not require additional blood sampling to complete. In addition, it may be a more accurate marker of iron overload, particularly in the presence of inflammation. RET-He measures iron available for erythropoiesis before anemia occurs by measuring iron on reticulocytes (Ennis, Dahl, Rao, Georgieff, 2018). Ennis, Dahl, Rao, Georgieff (2018) used this measure to determine inadequate levels of iron for brain development in animals. Remember that iron is used preferentially for red blood cell development rather than brain development. Therefore, low iron levels will impact brain development before anemia is seen. An additional study in progress (ClinicalTrials.gov NCT03169881) may also provide additional information about the usefulness of the RET-He measure as a valid measure of iron availability.

Iron supplementation

As mentioned earlier, iron transfer across the placenta happens during the third trimester of pregnancy. Delayed cord clamping has been thought to be beneficial in providing additional iron to the newborn. Das, Sundaram, Das (2018) reported on the effect of placental transfusion by delayed cord clamping (60 seconds) or cord milking on ferritin levels in preterm infants of 30-33 wks gestation at birth compared to early cord clamping. A significantly higher ferritin level was found at discharge in infants who received either delayed cord clamping or cord milking as compared to those who had early cord clamping. However, there was no significant difference in serum ferritin levels in these patients at three months of age, suggesting that supplemental iron is still needed in infants who benefit from additional placental transfusion through delayed cord clamping or cord milking.

Several guidelines exist concerning iron supplementation during infancy and childhood. The American Academy of Pediatrics (AAP) recommends initiating iron supplementation for preterm infants at 1 month, the Canadian Pediatric Society at 6-8 wks and the European Society of Pediatric Gastroenterology and Nutrition no later than 8 wks. The World Health Organization (WHO) (World Health Organization, 2016) recommends iron supplementation one, two or three times per week in pre-school and school age children. Amounts of recommended supplementation specifically for preterm infants vary somewhat as shown in Table 1. Although iron levels in human milk have been measured at about 0.35 mg/L, significantly less than what is in most infant formulas at 4-12 mg/L, it is better absorbed (Bjorklund et al, 2012; Lonnerdal, Georgieff, Hernell, 2015). The amount found in infant formula may be excessive for some infants and particularly term infants under 2 months of age.

Iron is particularly important for infants who may receive erythrocyte stimulating agents (ESA). ESAs are used to stimulate the production of red blood cells and may be given early in life, for that purpose as well as for neuroprotection (Ohls, Christensen, Schrader, 2013; Ohlsson, Aher, 2017). A few studies have evaluated the use of early intravenous iron particularly for these patients. Parenteral iron is available as iron dextran or iron sucrose. Iron sucrose is perhaps the more commonly used form but safety of both in neonates has been confirmed (Qiao, Tang, Zhu, Zhang et al, 2017; Pollak, Hayde, Widness, 2001; Mayhew, Quick, 1997; Ohls, Christensen, Lowe, 2013) Dosing of IV iron as reported by the studies mentioned here is varied:

- Qiao, Tang, Zhu, Zhang et al (2017) gave 2 mcg/kg/day for 2 weeks of iron sucrose,
- Ohls, Christensen, Lowe et al (2013) gave 3 mg/kg/week of iron dextran;
- Pollak, Hayde, Widness et al (2001) gave 2 mg/kg/day of iron sucrose.

German, Vu, Juul (2018) report on a sub-group of infants in an ESA study and iron needs. In this group of infants, iron was dosed at 5.4, 6.9 or 7.4 mg/kg/day enteral iron at 30, 60 and 90 days. Despite this iron supplementation that was significantly

higher than the dose recommended by the AAP, 66% of these infants had Ferritin levels less than 76 ng/mL. They theorize that higher doses of enteral iron, different preparations that are more digestible or intravenous iron may be more effective and necessary.

MacQueen, Baer, Christensen (2017) report on a performance improvement project they completed evaluating iron dosing in patients over a 10-year period in order to create iron guidelines to provide consistency in practice. While professional recommendations and guidelines provide a starting point, specific iron needs vary from one patient to another, making laboratory evaluation of iron levels key in avoiding either iron deficiency or iron overload.

Conclusion

The importance of iron in the developing neonate is well established. In order to ensure adequate availability, several measures are important. First, recognizing that iron stores are inadequate in premature infants and may be affected by other factors highlights the need for early and consistent supplementation. Second, iron dosing levels require further investigation as recommendations vary and levels studied vary. It is also important to have a reliable, simple measurement of iron availability in order to individualize iron dosing.

This article has focused on the needs of iron in the premature infant during hospitalization. It is important to remember that iron supplementation is recommended as the infant grows and develops through childhood by various organizations including the AAP and WHO (World Health Organization; 2016). Brain development continues during this time with periods of rapid growth when iron stores may be quickly utilized. Diet impacts available iron and must be considered as well.

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Choosing a Probiotic for Infant Use: Why Bacterial Strain Matters

Rebbeca M Duar, PhD and Tracy Shafizadeh, PhD

The composition and function of the gut microbiome in early life are deeply connected to infant growth, metabolic function, and nutritional and immunological development. Numerous environmental factors, including premature birth, cesarean delivery, as well as maternal and infant perinatal antibiotic exposure, can lead to major alterations in gut microbiome composition, also known as dysbiosis. Because the microbiome is so deeply intertwined with optimal infant development, aberrant microbiome compositions during this critical window may increase susceptibility to a variety of negative health outcomes, including, necrotizing enterocolitis (NEC), late onset sepsis, altered development of the immune system and physical growth.[1,2] Thus, ensuring a healthy microbiome composition in early life holds remarkable potential to improve a newborn's health trajectory.

Probiotics, which are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host,[3] have long been considered as a method to modify the composition of the infant gut microbiome. Potential benefits include limiting the growth of pathogenic species, restoration of beneficial functions to gut microbial communities and reduction of inflammation or other intestinal dysfunction related to dysbiosis.[1,4] However, all probiotic bacteria have a unique mechanism of action, and with an ever-expanding portfolio of probiotic products available, identifying the right one can be a daunting task to health care professionals and the public alike. Therefore, here we discuss two key aspects to consider when evaluating any probiotic for use in infants.

First, it is critically important for a probiotic to have a demonstrated mechanism of action in infants. Probiotic bacterial species that are naturally adapted to the infant gut are more likely to interact favorably with the immune system and have a better chance of establishing themselves at sufficient levels required to outcompete pathogens. For example, select species of bifidobacteria are naturally adapted to the infant gut and, in particular, *Bifodobacterium longum* subspecies *infantis (B. infantis)* is uniquely equipped to capture and metabolize human milk oligosaccharides (HMO) from breast milk in the infant gut.[5,6] Consequently, human milk is highly selective for *B. infantis* since 15% of the energy content of breast milk comes in the form of these complex carbohydrates. In recent clinical studies, *B. infantis* EVC001 fed to breastfed infants was shown to stably and persistently colonize the infant gut at high levels, resulting in a minimal loss of HMO in the stool and 80-90% lower levels of pathogenic bacteria compared to breastfed control infants who lacked *B. infantis*.[7] The mechanism of action of *B. infantis* in reducing pathogenic bacteria is therefore deeply connected to its unique ability to metabolize HMO, demonstrating that adaptation to the infant gut is a key consideration when selecting a probiotic appropriate for this specific age group.

… with an ever-expanding portfolio of probiotic products available, identifying the right one can be a daunting task to health care professionals and the public alike.

Second, it is also important to consider the bacterial strain when selecting a probiotic for infant use. Strains are subtypes of the same species and are classified based on genetic and biochemical properties that give each strain unique attributes. Not surprisingly, mounting evidence supports that the efficacy of probiotics can vary widely from strain to strain and the benefits observed with one strain cannot be extrapolated to another.[4,8] For this reason, international regulatory agencies such as the Food and Agriculture Organization/World Health Organization[9] recommend probiotic organisms be identified by the genus, species, subspecies (if applicable) and importantly, a strain designation. As mentioned previously, *B. infantis* is uniquely adapted to colonize the infant gut and metabolize HMOs from breast milk. However, not all strains of *B. infantis* can consume HMO to the same extent.[10] The strain *B. infants* EVC001 was isolated from the stool of a healthy breastfed infant, has been Generally Recognized as Safe (GRAS) for use in infants and is classified as a Food for Special Dietary Use under the FDA regulations. In clinical trials, *B. infantis* EVC001 has been shown to be well tolerated in breastfed infants and to efficiently colonize the infant gut resulting in significant reduction of pathogenic bacteria and enteric inflammation.[7,11,12] The unique mechanism of action of this strain allows *B. infantis* EVC001 to efficiently convert HMOs in breast milk to lactate and acetate in the infant gut. These organic acids not only contribute valuable fuel for the developing colonic epithelium, but also lower the fecal pH to a range that inhibits the growth of pathogenic and

Continued on page 26…

Rebbeca M Duar, PhD: Microbial Ecologist and Senior Microbiology Scientist at Evolve BioSystems. Tracy Shafizadeh, PhD: Nutritional Scientist and Director of Scientific Communications at Evolve BioSystems.

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Choosing a Probiotic…continued from page 24
inflammatory microbes. Conversely, when *B. infantis* is absent, these HMOs remain unmetabolized and are excreted in the stool rather than being converted to lactate and acetate.[7,13,14]

Of note, hospitalized infants are particularly susceptible to disruption of the successful establishment of a healthy gut microbiome due to the increased need for antibiotic and acid-reducing medications. Gut dysbiosis in this population has been linked to the development of NEC, late onset sepsis and poor growth.[2] Thus, establishing HMO-metabolizing strains of *B. infantis* with a demonstrated mechanisms of action (such as *B. infantis* EVC001) in the infant gut microbiome as the natural protection against the colonization of enteric pathogens has a great potential to improve the physical and immune development of hospitalized infants and may be key in achieving optimal health outcomes.

> …the efficacy of probiotics can vary widely from strain to strain and the benefits observed with one strain cannot be extrapolated to another .

In summary, the composition of the infant gut microbiome is an important factor in postnatal intestinal and immune development. Probiotics can be beneficial in establishing a functional gut microbiome in early life, but key information is needed when selecting a product for infant use. For the highest likelihood of success, be sure to ask two important questions: 1) is the bacterial species naturally adapted to colonize the infant gut and 2) is there a clinically-demonstrated mechanism of action in infants for the specific strain of bacteria provided? If the answer to both questions is not clearly yes, it's best to keep looking.

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Cost of Safety in Neonatal Practice: A Case Where Blood Was Ordered but Not Used

Shabih Manzar, MD

Blood is an expensive product. One unit of blood cost about US $210.74±38.[1] Not using the blood that is ordered is a healthcare waste. Physician play an important role in contribution to the health cost.[2] However, sometime safety decisions by physicians override the cost. We present a case of a premature infant in whom blood was ordered and not utilized resulted in waste of blood worth US $1000.

Case

A premature boy is delivered vaginally at 33-2/7 weeks to a 28-year-old gravida 2, para 0-2-0-3 mother. She presented to the labor and delivery unit in active labor. She did receive antenatal steroids and magnesium sulphate. All prenatal labs including RPR, HIV, hepatitis B, chlamydia and gonorrhea were negative. Rupture of membrane was at delivery with clear fluids. At delivery, infant had good cry and respiratory effort. Apgar score was 9 and 9 at one and five minutes respectively. Infant was placed in the incubator and transported to the neonatal intensive care unit (NICU).

On arrival to NICU, infant remained stable in room air. Vital signs showed a temperature of 98.6°F, heart rate of 152 beats per minute, blood pressure of 88/43 mm Hg, and oxygen saturations of 99%. Physical examination was normal, and he was appropriate for gestational age (weight 2230 grams, length 47 cm and head circumference 32.5 cm). At ~48 hours of life, he was noted to have a serum bilirubin of 13 mg/dL (222 µmol/L). Phototherapy was started immediately, and serial serum bilirubin levels were followed. The hemolytic workup resulting in unconjugated hyperbilirubinemia, including ABO and minor blood groups incompatibility, G6PD, pyruvate kinase and red cell smear morphology, were all negative. Reticulocyte counts ranged from 4-14%. On day 5 of life (~120 hours), despite intensive phototherapy, the bilirubin level reached 21.8 mg/dL (372 µmol/L). Serum albumin was 3.1 g/dL. Although, the infant continued to have a normal neurological examination and bilirubin: albumin ratio remained below the threshold for exchange, in view of the rising bilirubin, a decision of exchange transfusion was made. Parental consent was obtained, umbilical catheter inserted, and blood bank was called to arrange for sickle negative, CMV negative, irradiated, fresh, washed red cell. While receiving intensive phototherapy and awaiting reconstituted blood, the follow up serum bilirubin level went down to 19.6 mg/dL (335 µmol/L), which was below the exchange level. Intensive phototherapy was continued with gradual decrease in serum bilirubin level over time (Figure 1). A slight rise in bilirubin is noted on day 13th which corresponded to the blood transfusion that the infant received for symptomatic anemia, hemoglobin level of 7 g/dL. The cause of hemolysis remained obscure. Infant was discharged home to follow up with the pediatric hematologist.

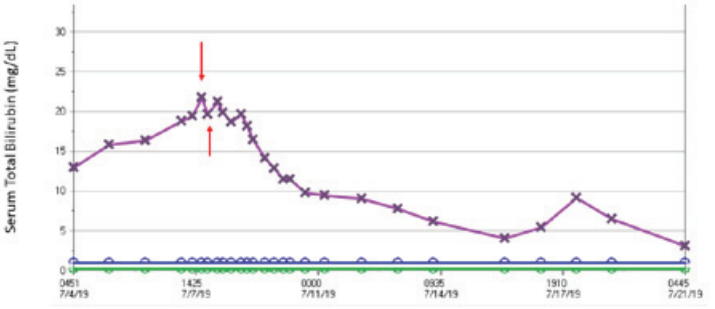

Figure 1. Graph showing serial Serum Bilirubin levels

Purple line: Infant's Bilirubin level;
Blue line and Green Line: Upper and Lower Normal Laboratory Values;
Red Arrow (downward): Decision for Exchange Transfusion was made;
Red Arrow (upward): Bilirubin level trended down;
Bilirubin is given as mg/dL (for conversation to µmol/L, SI, multiply by 17.1)

Discussion

Exchange transfusion (ETx) is an invasive procedure with potential complications.[3] Basing on available guidelines,[4-6] the threshold for ETx in the case was around 20-23 mg/dL (340-400µmol/L).We reserved the ETx as last resort since the infant had no immunological risk factor for hemolysis, had a B/A (bilirubin/albumin) ratio of 6.1 (6.8-7.2 is exchange threshold),[7] and normal neurological examination.

Neonatal ETx could be carried out with fresh or reconstituted blood.[8] Cross-matched fresh whole blood is not always readily available, and reconstitution takes time. By the time blood was arranged, the bilirubin had trended down. The reconstituted blood costed around US $1000, that was wasted. The decision of not transfusing blood resulted in saving the baby from the potential complications of blood transfusion but at the other resulted in wasting the precious blood.

Shabih Manzar is an Attending Neonatologist, Department of Pediatrics, College of Medicine, Louisiana State University of Health Sciences, 1501 Kings Highway, Shreveport, LA 71130. Address correspondence to Shabih Manzar, MD, 1501 Kings Highway, Shreveport, LA 71130, Telephone: 318-626-4374 Fax: 318-698-4305, Email: smanza@lsuhsc.edu.

Clinical decisions are not easy to make especially in cases where no concrete practice pathway is available. Should we have performed the exchange and saved the cost of blood once the infant had reached the threshold or had incidental delay in blood arrangement save the infant from exposure to blood product and its associated complications? The question remained to be answered. In conclusion, in healthcare, safety precedes cost. Some wastes are inevitable as seen in the reported case.

Acknowledgments

I would like to thank the blood bank for arrangement of blood products.

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Use of Umbilical Cord Proteins to Improve Surgical Scar Appearances

BM Petrikovsky MD, PhD

The long-term satisfaction with surgical procedures often depends on the appearance of the skin scar. The obvious advantage of laparoscopy and surgery via natural orifices, besides for a faster recovery, is minimal or no skin scarring.[1-3] Scarless wound healing has been observed in the fetuses of animals and humans.[4] In humans, the scarring of fetal wounds begins at approximately 24 weeks of gestation.[5]

Lately, in surgical subspecialties including obstetrics and gynecology, numerous attempts have been made to decrease scar formation and improve scar appearance. To date, clinical approaches to this problem range from molecular, mechanical, and drug-based therapies, along with engineered technology such as scaffolds and skin substitutes. However, these therapies are suboptimal and met with varying degrees of clinical success.

This report summarizes our experience with the use of a gel impregnated with Wharton jelly peptide P199, to stimulate host skin stem cells and improve scar healing and appearance. Wharton jelly peptide P199 is a known signal protein, which activates the host's own skin stem cells.[6,7]

Material and Methods

Patient satisfaction with scar healing was assessed 6 months after the surgical procedures using 0-10 scale. A score of 0 was assigned to minimal and 10 to maximum satisfaction with scar appearance. Twenty patients have had cesarean sections at term (primary 6, repeat – 14), Ten patients have had gynecological operations (hysterectomy in 6), two patients had the removal of tubo ovarian abscess, and two patients have had ectopic pregnancies. Elongated gel patches impregnated with Meso Wharton P199 were placed over the scar with instructions to use it for 6-12 hours a day for 3-6 months. When not used, gel patches were kept in a special pouch. Twenty-eight patients whose scars were not treated consisted of the control group. Patients of both groups were instructed not to expose their scars to direct sunlight for at least 6 months after surgery.

Table 1. Patient's satisfaction with the scar appearance

Number of Patients		
Study Group	**Control**	**Satisfaction Score**
14	4	8 – 10 *
12	4	6 – 7 *
5	12	4 – 5
4	8	3 and below

*P < 0.05
BM Petrikovsky is a paid lecturer for ABG Lab.

BM Petrikovsky is a Professor & former Chairman of Obstetrics and Gynecology, Nassau University Medical Center.

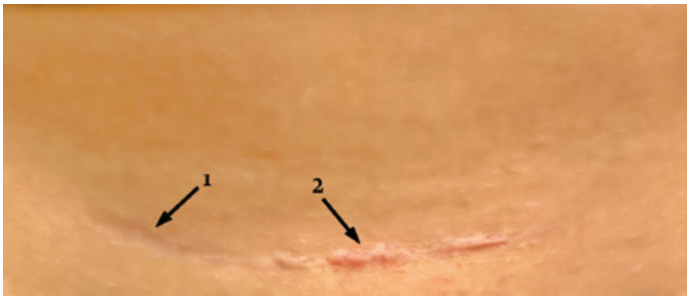

Figure 1. Partial scar treatment with patient consent.

The surgical scar with partial application of gel with P199. Solid arrow 1 marks the parts where the gel was applied. Solid arrow 2 marks the past that was not treated. Figure 1 demonstrates the efficacy of using P199 on the same patient with the same scar healing ability. Untreated areas were successfully treated later.

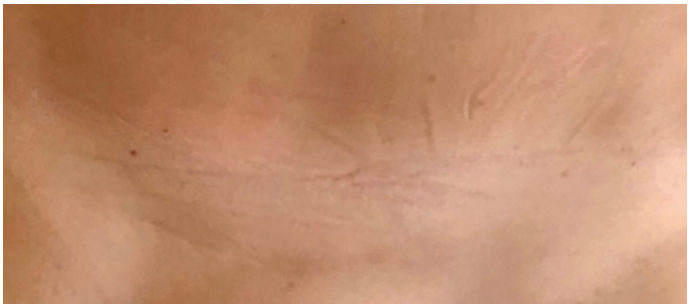

Figure 2. Appearance of the treated scar one year after surgery.

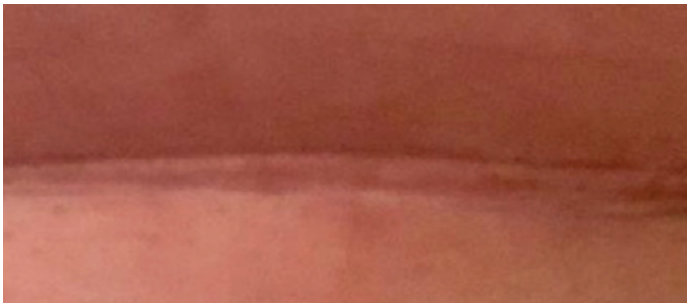

Figure 3. Untreated scar one year after surgery.

Table 2. Summary of adult versus fetal wound healing mechanisms

	Adult Wound Healing	Fetal Wound Healing
Collagen content	Predominance of type I collagen	Predominance of type III collagen
Adhesion proteins	Diminished up-regulation of adhesion proteins	Rapid up-regulation stimulates cell attachment and migration
Inflammatory cells	Many	Few
Interleukins	Rapid increase in cytokines (interleukin-6 and interleukin-8)	Increased expression of inflammatory cytokine (interleukin-10)
Gene expression	Delayed up-regulation of genes involved in cell growth and proliferation	Rapid up-regulation of genes involved in cell growth and proliferation
Stem cells	Skin stem cells found at low numbers to mediate scarless repair	Skin stem cells migrate to sites of injury and mediate scarless repair

Discussion

Numerous techniques have been suggested to improve patient satisfaction with the quality and appearance of postsurgical scars, including silicone, pulsed-dye laser, CO2 laser, corticosteroids, 5-fluorouracil, bleomycin, and scar massage, among others. Commercial creams and patches, including Biocorneum (Sientra), Mederma, Honeydew, Derma E scar gel, Cocoa butter formula, COS cream, Bio Oil, just to name a few, are available on the market. Khansa, et al.[8] analyzed evidence-based scar management techniques and reported low levels of patient satisfaction with the majority of remedies.[8] The probable reason is that these preparations do not change the mechanism of wound healing. Both fetal and adult wounds heal using collagen deposition. In fetal wounds, however, collagen is deposited in a fine reticular pattern indistinguishable from the surrounding tissue. In adult wounds, collagen is formed in densely arranged parallel bundles. All adult wounds heal with predominantly type I collagen, while fetal wounds heal with type III.

The production of inflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) are decreased in fetal skin in comparison with adult skin.[9-12] The levels of fetal immune cells, including macrophages, are reduced. In addition, the presence of inflammatory cells is shorter in the fetal wound healing process, in comparison with the adult.

Because fetal skin contains more hyaluronic acid than adult skin, several investigators have emphasized the role of hyaluronic acid in scarless healing.[12] Mesowharton has increases stem cell production thus converting the adult type of wound healing into the fetal type. Wounding stimulates an increase in interleukin-6 and interleukin-8, which persists at 72 hours in the adult but disappears by 12 hours in the fetus.[12-14]

Conclusion

Although scars can never be completely eliminated in adults, strategies aimed at converting healing favoring a fetal type of wound repair may be beneficial. Our experience with Meso Wharton P199 represents such an approach. Our study demonstrated a higher level of patient satisfaction in the treated group compared to the control group. The relatively small numbers prevented us from a detailed statistical analysis but the preliminary results are promising.

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Outcomes of Perinatal Multidisciplinary Engagement in an Urban Community Hospital Setting

Saminathan Anbalagan, MD[1], Kecia Gaither, MD[2], Andrej Bogojevic, MD[3], Jana Yancey, RDMS[4], Benamanahalli Rajegowda, MD[1]

Abstract

Background: Congenital anomalies continues to be a leading cause of death in-utero and in neonatal period. A risk oriented assessment requires a multidisciplinary approach to have positive perinatal outcomes. Aim of our study is to analyze the characteristics and outcomes of maternal-fetal conditions identified prenatally and referred to neonatologist as a part of multidisciplinary consultation in an urban community hospital.

Methods: Retrospective chart review of patients referred to neonatologist by Maternal-Fetal Medicine specialists at Lincoln Hospital, Bronx, NY between Jan 2017 to Dec 2018 (n=126). Maternal demographics, risk factors and outcomes of the pregnancy were noted. Prenatal fetal findings and postnatal neonatal findings were compared and analyzed.

Results: 97 out of 110 pregnancies resulted in live births. The most common congenital fetal anomaly was chromosomal (14.3%, n=18/126) followed by musculoskeletal (11.9% n=15/126) and renal (11.9% n=15/126). Out of the 18 chromosomal anomalies, only 2 pregnancies were terminated while rest were continued even though they were not viable. Besides major and minor congenital anomalies, 33% (n=42/126) had soft markers and majority of them had resolved in-utero.

Conclusions: Ultrasound soft markers should be interpreted with caution as the majority of them resolve with increasing gestational age. There is an increasing tendency to continue pregnancies despite the chromosomal anomalies and it is likely due to increased multidisciplinary support available for such parents by their family and religious beliefs.

Keywords: Congenital anomaly, Prenatal consultation, Multidisciplinary approach, Soft markers.

Introduction

Pre-pregnancy and early prenatal care serves to provide education, identify maternal or fetal problems, and guide appropriate management, ultimately impacting perinatal outcomes.[1] A risk-oriented assessment potentially requires a continued involvement with a host of providers across multiple disciplines — social work, ethicists, pastoral personnel, general obstetricians, geneticists, neonatologists, anesthesiologists, and in particular Maternal-Fetal Medicine (MFM) specialists. These specialists are expertly trained in high risk maternal-fetal conditions inclusive of medical diseases and prenatal diagnosis of fetal anomalies and genetic disorders, all of which impact the maternal-fetal dyad. Perinatal outcomes are positively influenced when a problem is identified early and multidisciplinary engagement is incorporated into the patient's prenatal care experience.[1-3] The objective of this study is to analyze the characteristics and outcomes of maternal-fetal conditions identified prenatally and referred to neonatologists by MFM specialists. A detailed review of prenatal identification of congenital anomalies (CA) in a multidisciplinary setting is vital because CA remains the leading cause of in utero/neonatal death in the United States (US).[4]

Methodology

Lincoln Medical and Mental Health Center in the Bronx, NY is a Level III Perinatal Center serving a high risk urban population comprised of predominantly Hispanic, African American, and a burgeoning immigrant population. The Joint Commission recently designed our institution as a Regional Perinatal Care Center and as a Perinatal Center of Excellence. We have a designated maternal-fetal diagnostic center staffed with two MFM specialists and support services. The perinatologists perform pre-conceptual counseling along with plenty of maternal and fetal testing throughout all trimesters of pregnancy — invasive testing like amniocentesis, noninvasive prenatal testings' (NIPT), first, second and third trimester sonography, along with fetal well-being assessments. Issues related to maternal-fetal condition that were diagnosed using any of these methods were managed by appropriate interdisciplinary team and comprehensive counseling was provided for the mother and the family.

Our study is a retrospective chart review done over two year period between Jan 2017 and Dec 2018. The study was approved by our Institutional Review Board (IRB) with waiver of consent. We reviewed the charts of all patients with prenatally identified complications that were assessed by MFM specialists and reported to the neonatology team for further follow-up and counseling. The reasons for referral included any congenital/genetic anomaly identified in the fetus via prenatal diagnosis, maternal high risk medical conditions, or both. Baseline details of the mother like demographics, gestational age at diagnosis,

[1]Department of Pediatrics, [2]Department of Maternal-Fetal Medicine, [3]Department of Genetics, [4]Department of Radiology. Lincoln Medical and Mental Health Center, Bronx, NY, which is affiliated to Weill Cornell University, NY. Corresponding Author: Saminathan Anbalagan, MD, Lincoln Medical and Mental Health Center, affiliated to Weill Cornell University, 234 E 149th St, Bronx, New York 10451 Email: sswami189@yahoo.co.in

and maternal risk factors were obtained. Outcomes of the pregnancy among those who delivered and postnatal findings in the neonate were also noted. Both prenatal and postnatal findings were compared, and the results were tabulated. Congenital anomalies in the fetus were classified according to the systems involved.

Results

A total of 126 maternal-fetal-infant charts were reviewed. The majority of the population were Hispanic (n=77) and African American (n=44). The maternal age was advanced in 30.1% (n=38/126) of the study population. At the time of data analysis, ten mothers were lost to follow up after the diagnosis of the congenital anomaly (3 musculoskeletal anomalies, 2 cardiac, 2 fetal growth, 1 pulmonary, 1 renal and 1 multisystem) and six mothers were still pregnant. Eight mothers were transferred to tertiary medical centers for a higher level of care which was unavailable at our institution and they were also included in the data analysis. Out of the transfers, 3 pregnancies resulted in a live birth, 2 Intra Uterine Fetal Demise (IUFD), 2 were still pregnant at the time of analysis, and 1 lost to follow up. 97 out of 110 pregnancies (88.1%) resulted in live births and 95 of them delivered at Lincoln Hospital. Three mothers decided to terminate the pregnancy due to multiple severe anomalies, and 2 of those fetuses had chromosomal anomalies (One Trisomy 21 and One Trisomy 18). Eight fetuses deceased in utero (IUFD) and 87.5% (n=8) was due to chromosomal abnormalities (Four Trisomy 21, One Trisomy 21 with XYY and Two Trisomy 18). Two mothers had spontaneous abortions, and one of them was due to Trisomy 18; both these mothers had significant risk factors like advanced maternal age and obesity. Both major and minor congenital anomalies identified prenatally and referred to the neonatologist are tabulated (Table 1). The most common system involved was chromosomal (14.3%, n=18/126) followed by musculoskeletal (11.9% n=15/126) and renal (11.9% n=15/126) in order of frequency, as shown in Table 1.

Discussion

About 3-5% of pregnancies in the US result in babies with birth defects or genetic abnormalities.[4] Hence it is crucial to identify these anomalies prenatally. Prenatal testing is done for several reasons, but its main objectives are the following: To provide the family with the details of the congenital anomaly and what the family can expect during pregnancy, delivery and after birth. To provide timely fetal interventions in utero, either prophylactically or therapeutically. To prepare the family mentally, medically, socially, and financially for a baby with a birth defect or genetic problem. To provide interventions for the anomaly either pre- or post-natally. To determine the appropriate place and type of delivery. To give the family an option to choose termination of pregnancy, especially in the cases of potentially lethal conditions. It also affords the input of a multidisciplinary team, inclusive of a perinatologist, neonatologist and pediatric surgeon, to be present and well prepared for the delivery of the newborn that may require early medical and or surgical management.[1] Our team at Lincoln hospital made use of the objectives of these testing and provided the appropriate intervention at every level as needed.

Prenatal diagnostic testing can be either for screening or diagnostic/confirmatory purposes. It is broadly classified into imaging and maternal serum testing. These tests have evolved and so has the interventions that are done in-utero. Historically, prenatal ultrasound was done only when needed, based on risk factors and at the discretion of the physician. However, now it has evolved as a routine evaluation in the developed world. In the US, the American College of Obstetricians and Gynecologists (ACOG) recommends at least one ultrasonography (USG) during pregnancy to rule out fetal anomalies, between 18-22 weeks of pregnancy.[5] Routine ultrasound during pregnancy screens for fetal malformations and the majority of it is generally identified in the second trimester. In our study, USG was found to be the most common modality for the identification of the congenital structural anomaly and 82.5% (n=104/126) of the anomalies were detected in the second trimester, reiterating the importance of the scanning for fetal anomalies in second trimester.[6,7] The most common anomaly identified in this study was aneuploidy, followed by musculoskeletal, renal, and GI in the order shown in Table 1.

Since the advent of routine ultrasound screening in the developed world, minor anomalies have been detected with increased frequency. Even though these anomalies are minor and may represent a normal variant (false positive), they may be correlated with severe fetal chromosomal aberrations or genetic abnormalities (true positive). Such minor ultrasound findings are termed "soft makers" (SM). Some of the SM includes an enlarged nuchal translucency, cystic hygroma or short nasal bone in the first trimester, and echogenic intracardiac foci, pyelectasis, echogenic bowel/organs, thickened nuchal fold or mild cerebral ventriculomegaly in the second trimester.[8,9] In our study, other than major structural anomalies identified, a significant number of fetuses had one or more SM (33%, n=42/126) and the majority had resolved in-utero. Several chromosomal anomalies were associated with more than one of the above SM (7 out of 18) concurring with the ACOG's bulletin.[8] Many studies[10-12] have reported that the presence of only a single SM has a low likelihood ratio. However, the recommendation is to evaluate for chromosomal or genetic anomalies based on other risk factors. Our study's result also matches those findings,[10-12] as the majority of single SM resolved in utero and were not identified postnatally. Sylvie Viaux et al.[13] reported that false positive soft markers resulted in increased maternal anxiety and depression, thus affecting the mother's interaction with the infant in a crucial development period. In our institution, after the multidisciplinary consultation, every step was taken to decrease this effect. Babies with single fetal SM that resolved in-utero were assessed by neonatal examination and the mother was informed immediately about the normal findings to allay apprehension.

Besides USG, other imaging that are available for confirming or refuting anomalies diagnosed by USG include fetal ECHO and fetal MRI. In our study, all cases of cardiac anomalies identified by screening ultrasound were referred to a pediatric cardiologist who performed the fetal ECHO. Those that required fetal MRI were transferred to tertiary care centers where the equipment was available; those included CNS (2), GI (1), reproductive (1) and lung anomalies (1).

Invasive methods like Chorionic Villus Sampling (CVS) and Amniocentesis are still being done as confirmatory tests for aneuploidy, but the focus has moved towards more noninvasive testing NIPT.[14] Many new modalities of noninvasive testing are becoming available for the diagnosis of fetal conditions; as an example- genetic testing like Single-Nucleotide Polymorphism (SNP), digital Polymerase Chain Reaction (PCR). Additionally, genomics-based noninvasive prenatal testing such as massive parallel shotgun sequencing (MPSS) and targeted massively

Table 1. Classification of congenital anomalies based on system involved and its outcomes.

System	No. identified prenatally. (Major and Minor anomalies including soft markers)	No. of soft markers	No. followed up	No. lost to follow up	No. Still pregnant at the time of analysis	No. terminated/ aborted/IUFD	No. identified postnatally
GI	14	7	13	0	1	0	1*
Cardiac	14	4	11	2	1	0	5**
Chromosomal	18	7	6	0	1	11	5***
Musculoskeletal	15	4	12	3	0	0	10****
Neurological	8	4	7	0	1	0	2^
Fetal growth	7	-	5	2	0	0	3^^
Pulmonary	4	3	3	1	0	0	1^^^
Renal	15	8	14	1	0	0	6^^^^
Genital/ Reproductive	2	-	2	0	0	0	2^^^^^
Multisystem	5	5	2	1	1	1	2
Umbilical cord	7	-	7	0	0	0	0
Placenta	4	-	4	0	0	0	-
Maternal causes: No prenatal fetal congenital anomalies	13	-	11	0	1	1	-

*1 Omphalocele was identified prenatally & confirmed postnatally.
**4 VSD & 1 multiple cardiac anomalies identified prenatally & confirmed postnatally.
***1 Trisomy 21, 1-XO, 1-5p deletion, 1-XYY, 1-XXY were identified prenatally & confirmed postnatally.
****4 Talipes equinovarus and 3 cleft lip and/or palate, 2 skeletal dysplasia and 1 limb defect were identified prenatally & confirmed postnatally.
^1 Lagging BPD and 1 macrocephaly were identified prenatally & confirmed postnatally.
^^2 IUGR and 1 macrosomia were identified prenatally & confirmed postnatally.
^^^1 Lung cyst was identified prenatally & confirmed postnatally.
^^^^2 Atretic kidney, 2 pyelectasis, 1 hydronephrosis, and 1 polycystic kidney were identified prenatally & confirmed postnatally.
^^^^^2 Ovarian cysts were identified prenatally & confirmed postnatally.

parallel sequencing (TMPS) are finding their way into the perinatologists' collection of offered options.[15] More and more conditions are being diagnosed early in pregnancy, particularly in the genetic field, leading to improved maternal knowledge of fetal conditions and improved outcomes in pregnancies. While these diagnostic studies have improved the detection of chromosomal anomalies, the rates of termination have remained relatively stable over the years.[16,17] We found in our study that the majority of the pregnancies diagnosed with chromosomal anomalies were continued with only 2 of them deciding to terminate the pregnancy (1 trisomy 21 and 1 XO Turner syndrome). We postulate that the trend to continue the pregnancy despite the chromosomal anomalies may be due to increased multidisciplinary support available for such parents by their family and religious beliefs. Of note in our study, even though the pregnancies were continued after the diagnosis of chromosomal anomalies, the majority of the pregnancies were not viable, resulting in fetal demise or spontaneous abortion.

The limitations of this study include the nature of study which is retrospective chart review, small study sample, lack of control subjects and single center study. The presence of a single pediatric cardiologist at our center may have resulted in selection bias. Outcomes of pregnancies without multidisciplinary consultation were not analyzed.

Conclusion

Whenever a congenital fetal anomaly is identified in the antenatal testing, it is imperative to discuss the risks, accuracy, and validity of the screening or diagnostic test. It should also include the risk of miscarriage from invasive procedures such as CVS/amniocentesis, as they are known to be associated with a small but increased risk of pregnancy loss. Our study found that ultrasound soft markers are being detected with increasing incidence and should be interpreted with caution as the majority resolves with increasing gestational age. Chromosomal, musculoskeletal and renal anomalies were the most common fetal anomalies. Medical and ethical issues such as continuing pregnancy versus termination should be left solely to the legal caregivers after complete, precise details are provided. For that, a multidisciplinary approach is required, especially in multiple congenital anomalies. Our study found that there is a tendency to continue pregnancies despite the chromosomal anomalies and it is likely due to increased multidisciplinary support available for such parents by their family and religious beliefs. It is crucial to explore the parent's understanding of the CA, provide goals of the consultation, and discuss the anomaly and its prognosis after gathering all information from other consultants also. It is a must, to also include discussion about the place of birth, type of delivery, risk of perinatal death, the potential need for resuscitation, NICU admission, and NICU course inclusive of postnatal procedures feeding practices, and long term morbidities. Additionally, it is essential to arrange for psychosocial support to the family during the NICU stay and post-discharge. These modalities are most helpful in having a positive perinatal outcome for both mother and baby.

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Delivering Complex Care for Complex Children: A Multidisciplinary Approach

Matthew T Brigger, MD, MPH and Kimberly Morris, MS, CCC-SLP, BCS-S, IBCLC

An increasingly visible trend exists regarding efforts to improve the care of children with complex aerodigestive disorders. For many years and a variety of reasons, children with complex disorders have often been cared for in tertiary referral centers. Such centers have provided the availability of a wide range of subspecialty care. Multidisciplinary care centers have existed for many years to treat children with craniofacial anomalies, cystic fibrosis, and cancer. However, recently, pediatric aerodigestive centers have had increasing visibility and marketing presence. As such, it is important to understand who is involved, why such centers exist, and what it means.

Complex care for complex children

Children with upper aerodigestive issues have a wide range of presentations, as well as degrees of severity. The spectrum of such disorders ranges from simple allergic rhinitis, associated with mild asthma, to tracheostomy-dependent former NICU graduates with a limited pulmonary reserve and a myriad of congenital anomalies. Regardless of the severity of such disorders, these children require care by a variety of both generalists and specialists.

The consensus statement by Boesch et al. (2018) provided an excellent description of the pediatric aerodigestive patient as:

A child with a combination of multiple and interrelated congenital and/or acquired conditions affecting airway, breathing, feeding, swallowing, or growth that require a coordinated interdisciplinary diagnostic and therapeutic approach to achieve optimal outcomes. This includes (but is not limited to) structural and functional airway and upper gastrointestinal tract disease, lung disease because of congenital or developmental abnormality or injury, swallowing dysfunction, feeding problems, genetic diseases, and neurodevelopmental disability (p. 3).[1]

Delivering multidisciplinary care within other settings may be difficult which is a . A basic premise is that better outcomes will be achieved by avoiding fractionalized care. The trend of increased visibility provides an opportunity for children with a full range of presentations to receive multidisciplinary care. An additional benefit of coordinated care allows a collective experience with developing both basic science and clinical research initiatives to better understand disease processes and further improve care.

Who is involved?

Central to the care of children with upper aerodigestive problems are a pediatric otolaryngologist, pulmonologist, and gastroenterologist. From a coordination standpoint, the otolaryngologist often serves as a central figure as their anatomical area of expertise represents the junction between the disciplines. Additionally, the care of such children often requires access to speech-language pathologists with specific interests in swallowing and possibly even voice disorders.

Furthermore, an allergist can provide much-needed insight and treatment for children with atypical allergy symptoms. Access to nutritionists and a feeding team provide valuable resources for determining nutritional needs and feeding/swallowing efficiency for intake with this patient population. At times, the team will include pediatric anesthesiologists with experience in spontaneous ventilation anesthesia techniques and access to a pediatric intensive care unit, if a child is to undergo the full range of operative airway care. The involvement of a strong support staff of case management, social work, and nursing ensures that once the children are discharged, they continue to receive the necessary care.

What are some common conditions that are treated?

A wide variety of conditions affecting the aerodigestive tract are within the scope of therapy for coordinated multidisciplinary care. Airway obstruction secondary to congenital or acquired anomalies, atypical reflux disease, chronic cough, aspiration, allergic conditions, as well as feeding and voice disorders, are

Dr Matthew T Brigger is Chief of the Division of Otolaryngology at Rady Children's Hospital-San Diego and Associate Professor of Surgery at UC San Diego School of Medicine. His primary clinical interests are diseases of the upper aerodigestive tract, with a focus on surgical management of children with breathing and swallowing disorders. Dr. Brigger conducts research on treatment outcomes for children with breathing and swallowing disorders and has authored over 60 peer-reviewed studies. He presents at national and international meetings. Kimberly Morris, practicing since 2006, evaluates and treats patients with feeding and swallowing impairments, as well as cognitive-communication impairments in neonates through young adults. Kimberly joined Rady Children's Hospital San Diego in 2018, after previously working at Al duPont Hospital for Children and Miller Children's Hospital Long Beach. She conducts FEES assessments and is a Modified Barium Swallow Impairment Profile (MBSImP) registered clinician. She also participates in national research initiatives to optimize dysphagia outcomes for neonates with congenital heart disease and for children who are tracheostomy-dependent.

commonly evaluated and treated.[2] Complex presentations, or children with multiple medical problems, are particularly well suited to this care model.

How do aerodigestive centers facilitate care for children who have tracheostomies?

The genesis of medical complexities that ultimately lead a family and medical team to decide on tracheostomy placement is variable. Watters (2017), following a survey of 36 children's hospitals, indicated that chronic lung disease (56%), neurological impairment (48%), and upper-airway anomaly (47%) are the most common underlying comorbid conditions in children 0-18 years of age, who undergo tracheostomy.[3] However, a common binding factor for these children is needed, specifically, a medical team who identifies the barriers and facilitates interventions that may aid in eventual decannulation. When tracheostomy placement does not have foreseeable options for decannulation, ongoing discussions should still occur regarding medical and therapeutic management for each child.

The aerodigestive team values accountability for assessing and identifying the barriers to decannulation, as it is the unique role of each discipline to facilitate this process. This often includes debunking theories held by individuals on the team, including the extended healthcare community, because these myths limit the optimization of care (eg, a cuff remaining inflated because of known dysphagia and aspiration risk; poor weaning from the ventilator because of vocal cord paresis; gastroesophageal reflux as a primary factor for poor pulmonary status; inability to trial food by mouth (PO) because of "aspiration on an instrumental assessment," and more). Although the previously stated scenarios are important discussion points for the aerodigestive team, the relevance of each concern may be highlighted, and the direction of care steered to achieve expedited progression of care. This may include immediate trials of partial cuff deflation during the visit to assess how swallow function changes when gaining access to the upper airway; use of Flexible Endoscopic Evaluation of Swallowing (FEES), to look at vocal cord function and secretion management; obtaining transtracheal pressure measurements, to assess upper airway access and efficiency of respiration; Passy Muir Valve or capping trials; decannulation during the visit; or even admission to facilitate establishment of a more thorough care plan. Throughout each appointment, the team communicates and orders the necessary ancillary testing or interventions deemed necessary to facilitate optimal outcomes for each child.

Optimizing dysphagia management for children with tracheostomies and ventilator dependency

The etiology of pediatric feeding and swallowing difficulties may arise from a variety of airway problems, including laryngomalacia, vocal fold paralysis or paresis, laryngomalacia, laryngeal cleft, choanal atresia or stenosis, facial hypoplasia, subglottic stenosis, as well as CNS and neuromuscular diagnoses. When considering the complexity of having a tracheostomy tube and the known increased risks of adverse events and mortality, a multidisciplinary approach to dysphagia is even more critical.[4]

The potential effects of a tracheostomy tube on the aerodigestive system are well supported in the literature, including reduced laryngeal movement; aphonia; slower and reduced airway closure during the swallow;reduced cricopharyngeal opening[5]; and tethering of the larynx during the swallow, when cuff pressures are not properly managed.[6] Additional impacts include reduced airflow to the upper airway, leading to reduced laryngeal sensation and increased pooling of secretions; alteration in subglottic pressure, affecting neuro-regulation and oropharyngeal swallowing physiology[7]; loss of pressure, impacting breath support;decreased Positive End-Expiratory Pressure, leading to decreased ventilation of the alveoli (contributes to atelectasis)[8]; and reduced ability to expectorate secretions and to cough effectively.[9] With an open system, loss of pressure within the thoracic and abdominal cavities also may impair core strength and stability, causing bowel movements to be more difficult and potentially increasing constipation.[10]

Having an aerodigestive team can speed the diagnosis and treatment of dysphagia for children with tracheostomy dependence. Focus is placed on helping children regain access to their upper airway to optimize the achievement of their ideal health and aerodigestive potential, which includes establishing the least restrictive diet. Key components of the multidisciplinary visit that uniquely facilitate feeding and swallowing outcomes in children with tracheostomy dependence include:

- Assessment of oropharyngeal swallowing status via clinical examination, including secretion management and response to facilitative swallowing strategies that may reduce suctioning needs.
- Establishment or modification of oral care plans.
- Instrumental assessments (FEES/ Modified Barium Swallow Study), when appropriate.
- Assessment of cuff status and management with a clear reason and plan, if cuff needs to be inflated.
- Thorough assessment for Passy Muir® Tracheostomy & Ventilator Swallowing and Speaking Valve candidacy and rapid troubleshooting when tolerance of the Valve is not achieved.
- Assessments include the use of clinical airway and dysphagia evaluations by the team; use of transtracheal pressure manometry to determine end-expiratory pressures during Valve or capping use; direct visualization of airway via instrumental examination (at times including FEES);, and recommendation of more invasive diagnostic procedures.
- Establishment of a plan to optimize access to swallowing skills and upper airway, if unrestricted cuff deflation or use of Passy Muir® Valve cannot be prescribed by the end of the visit.

Does it need to be in a "center"?

Despite the recent popularity of such aerodigestive centers, the cornerstone of comprehensive care for these children is the active communication that occurs between providers. Furthermore, each provider must understand and have a common perception of the upper aerodigestive tract as a unified system, where there is a complex interaction between the gastrointestinal tract and the upper and lower airways. As such, though a center may allow for easier coordination of higher patient volumes, it is not necessary. Excellent care for these children may certainly be accomplished in a setting where active communication lines exist between subspecialists.

When do I refer?

Referral patterns are dependent upon your area of expertise, availability of pediatric subspecialists, and community resources. General guidelines for referrals include children with complex medical backgrounds and with aerodigestive symptoms that fail to subside with routine therapies. Furthermore, it may be useful to refer children who have airway symptoms that are on the mild end of the spectrum but have persistent difficulties. Many

children seen in these clinics present with persistent symptoms, such as a chronic cough with no clear etiology, and only a multidisciplinary evaluation results in a unifying diagnosis. In some cases, a comprehensive evaluation may solidify the diagnosis and provide confidence in the devised treatment plan.

Bringing it all together

The recent attention to such pediatric aerodigestive centers highlights something that has occurred in the care of medically complex children for many years. Multidisciplinary coordination is a vital aspect in the care of children. It is important to realize that the concept is not new. As stated above, such centers have existed for the care of children with craniofacial anomalies, cystic fibrosis, and cancer care for many years. The recent attention serves to highlight the importance of comprehensive multidisciplinary pediatric care in patients with complex aerodigestive system disorders.

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PICC Lines – Waterproofing & Securement on Neonates

Michael Todd Sapko, MD, PhD

A peripherally inserted central catheter (PICC line) is a long, thin tube that is inserted into a vein in the right upper arm and extends to the superior vena cava, just outside the heart. PICC lines usually have two ports through which fluids, medications, and blood products can be infused. PICC lines allow patients to continue IV therapy at home—something that cannot be safely accomplished with standard IV catheters or traditional central lines. While PICC lines are generally safe for home use, proper PICC line securement and use are essential.

Why are PICC lines used in medicine?

In a hospital setting, intravenous (IV) medications are infused through a standard, short IV catheter. This is the typical IV catheter used in virtually every hospitalized patient. Standard IV catheters are great for most applications, but they are not useful in two situations. Standard IV catheters cannot be used to infuse medications that irritate veins, nor are they safe for repeated, at-home IV infusions.

Some medications are irritating to veins if they are infused through standard IV catheters. The veins in the arm or leg are so narrow that if drug was infused through a standard IV catheter, it would cause pain and inflammation at the IV site. Because they are so short, standard IV catheters aren't very secure and tend to move out of the vein. This makes them impractical for long-term use.

Healthcare professionals overcome this problem by using PICC lines, which are long catheters that extend from the arm vein to a large blood vessel near the heart. PICC lines are useful because even irritating medications infused through these lines do not irritate large diameter veins near the heart. PICC lines are safer for home use than traditional central lines because they enter the body through small peripheral veins rather than large central veins. PICC lines are also much more secure and stable than short IV catheters, and can standup to weeks of repeated use.

Michael Todd Sapko, MD, PhD, completed a dual MD/PhD program at the University of Maryland with a PhD in neuroscience. After an internship in internal medicine in Baltimore, Dr Sapko embarked on a career in medical writing. Over the past 12 years, he has written hundreds of physician- and patient-facing materials including patient brochures, continuing medical education programs, peer-reviewed journal articles, and white papers. One of Dr Sapko's scientific interests is in understanding how diabetes and hyperglycemia interfere with wound healing and peripheral nerve function.

PICC lines are used in several conditions

PICC lines are used to infuse certain IV medications and blood products. Any neonate who is less than 1,250 grams, requiring antibiotics or total parental nutrition for more than 5 days is an obvious candidate. An infant over 1,000 grams requiring frequent blood draws could be considered for a larger PICC as the unit I work in uses the line for blood drawing as well as fluids and antibiotics. Another common reason to use a PICC line is to administer total parental nutrition or TPN. Total parental nutrition is a mixture of carbohydrates, proteins, fats, vitamins, and minerals that are administered intravenously. TPN can provide nutrition for those who cannot eat food by mouth.

Someone may have a PICC line placed if they need ongoing IV therapy but have no other reason to stay in the hospital. A PICC line is usually placed if the patient needs IV therapy for more than a few days, up to 6 months.[1]

Why PICC lines fail

PICC lines are excellent choices for intermediate-term venous access, but the proper use of PICC lines is essential to keep them from failing. PICC lines can fail (and usually must be removed) for several reasons.[2]

- **Infection** – Since the catheter passes through the skin and enters the bloodstream, there is always some risk of infection (eg catheter-associated bloodstream infection or CABSI). Patients and caregivers should be meticulous about keeping the tip of the PICC line as close to sterile as possible. Caregivers should touch the PICC line as little as possible, and only do so with clean, gloved hands.
- **Phlebitis** – The catheter itself may irritate the vein, causing phlebitis. Keeping the PICC line immobile may reduce the risk of phlebitis. Phlebitis can sometimes be treated with NSAIDs and warm compresses (ie PICC removal may not be needed).[1]
- **Occlusion** – The catheter may become occluded (blocked) for three reasons: blood clots, drug precipitates, malposition. Properly flushing the line can reduce the risk of blood clots and medication precipitation, while proper PICC line securement can reduce the risk of malposition.
- **Catheter Migration** – Catheter migration occurs when the tip of the PICC line moves out of its intended position. It may occur during placement (primary migration) or afterwards (secondary migration). Proper PICC line securement can prevent catheter tip migration.[1]

Primary and secondary PICC line securement

As you can see, proper PICC line securement can help reduce

the risk of several types of PICC line failure including secondary catheter migration, occlusion through malposition, and phlebitis. PICC lines are not "tunneled," so securement and stabilization depend on how well the healthcare professional can anchor the end of the line to the arm. In truth, medical tape must do all of the work of stabilizing the end of the PICC line.

Carol Czajka, BSN, RN, CPN, VA-BC and colleagues have discussed the importance of both primary and secondary PICC line securement. Primary PICC line securement—sometimes called stabilization—is the medical adhesives that hold the end of the PICC line in place. Secondary PICC line securement, on the other hand, are the steps taken to prevent other lines from pulling on the catheter. For example, a clear adhesive covering may be used as primary securement to keep the external end of the PICC line firmly attached to the skin. Medical tape is then used to reinforce the primary securement and anchor the IV lines that are attached to PICC line. Primary securement cannot withstand the force of IV lines being caught on a bed rail and pulled, but secondary reinforcement can. Both primary and secondary PICC line reinforcement are critical to ongoing successful PICC line use.

Hy-Tape is the ideal medical tape for secondary securement of PICC lines

Hy-Tape—The Original Pink Tape®—is strong enough to provide excellent secondary securement for PICC lines. It conforms to the shape of skin surfaces and adheres even more tightly as it warms to body temperature. Despite its strength, Hy-Tape releases cleanly and with little to no skin trauma. This, it can be easily removed from lines and skin. This is important, because any medical tape used for PICC line securement must be strong on lines, but gentle on skin.

Hy-Tape may be useful for primary PICC line securement

While clear dressings are commonly used for primary PICC line securement, they contain latex and adhesives that may provoke allergic reactions. An allergic reaction at a PICC line site can have devastating consequences since the area can become so inflamed that no adhesives can be used. No adhesives mean no securement, and no securement means no PICC line.

Because Hy-Tape is latex free and has a soothing, zinc-oxide based adhesive, it can be used as primary PICC line securement for patients with a documented or suspected latex allergy or otherwise sensitive skin. Healthcare professionals can use Hy-Tape under and over the exposed PICC line to stabilize it on the skin while still allowing free access to the PICC line ports. As discussed previously, Hy-Tape can also be sued for secondary PICC line securement.

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The End of an Error – Part 3

Kelley Karp MSN, BS RN

Introduction

Part 1 of "The End of an Error" covered the cognitive failures and mental validations that impact the potential for error.

In part 2, we focused on how human factors influence processes and contribute to errors as well as detailed some examples of failure points.

In Part 3 we will discuss the current state of electronic management of infant feeding and opportunities to improve safety in these processes.

Baby-Bottle Scan Insufficiency

Many institutions (or are being mandated to) employ EMRs that treat breast milk as a medication in an effort to check the safety box and move on. While we can all, philosophically and clinically, agree this to be true, it is extremely lacking when considered in terms of safety management.

Why are EMRS not stepping up? Well they are, however, most EMRs utilize their existing medication management system as a proxy for infant feeding safety scanning. Is this better than nothing? Absolutely, but building on the medication module does (or does not do) a number of things.

To utilize the scanning functionality often infant feeding orders have to be built as medication orders. Medication orders are typically fairly standard. These builds do not allow for the complex recipes and feeding regimens that we all use. With a standard tech platform, heavy customizations of functionality need to occur and I think we can all agree that competing for institutional IT resources is a herculean task in the best-case scenario.

These systems simply provide the final confirmation of a baby-to-bottle match during feeding, which although a critical step, misses the multitude of other preparatory steps - each as important as the one before it. You do not have the ability to track issues along the prep path, evaluate practice and make improvements. If nothing else it is a false sense of security for families and staff.

- Some of the processes that are missed
- Patient verification
- EBM/DHM state change rules
- Recipe calculations and verification
- Expiration verifications
- Feeding order validation at administration

The cognitive failures and mental validations are back to haunt us.

As we have continued to explore, infant feeding management is extraordinarily complex and involves multiple processes and players. Isn't it unusual to have a complex process without some mandatory and/or regulated process around it?

Bar Code Medication Administration (BCMA) is the most established process that we can compare infant feeding scanning to. Remember that BCMA is a CMS core measure with an incentive program.

Let's take a quick look at the similarities and differences. To meet the requirement institutions have to be able to electronically document the "5 rights" of medication administration. I am not trying to downplay the criticality or the significance of each of these steps. But it is far fewer than what we need for feeding administration and this list grows when you are talking about the integration of scanning technology and its capabilities or needs thereof. Also, medication administration is a standardized process. Follow your 5 rights for safe medication administration often now including a scanning step. Infant feeding management is so complex and every institution does it differently.

Leadership Challenges

What steps can we take to change the culture around feeding management safety? How do we as leaders help others understand these issues need attention?

Establishing and leading a culture of safety, more specifically safe communication. We need to realize that oversight and monitoring for rule compliance are never-ending and in some circumstances incredibly difficult to do, but that does not make them unnecessary. We need to be attentive to signals from our staff and never assume that policies are procedures are always being followed to the letter.

Validation of need — We each need to look at our institutional practices complete our own FMEA, process mapping, error rates

Kelley Karp is a Clinical Director at Keriton. Website: www.Keriton.com. Telephone: +1-267-307-7657. Email: kelley@keriton.com.

evaluation etc. and publish. As we have discussed there is very little research on the true state of these issues or validate that there are any.

Consensus — We need to come together, data in hand, and truly talk about standards of care and establish the best practices

Research — Do it and publish it. Get the conversations started and the eyes and ears open to your cause.

Conclusion

What impacts errors and our ability to detect and prevent them continues to be a complex conversation. Throughout this series, we have worked through some of the pieces to this puzzle. We have reviewed cognitive reasons errors occur — distractions, prospective memory, cognitive fatigue, inattentional blindness, and mental validations.

We then looked at the normalization of deviance, active and latent errors and the day to day workflows and operational challenges experienced by staff. Amongst all the distractions and mental validations, we are relying on humans to not only detect but prevent dozens of potential failure points, the majority of which go undetected, unappreciated, unreported, and unresolved.

So now we are back to our problem statement. **To date, there exist no universally accepted, national guidelines or standards that regulate the safety management of preparation and administration of infant feedings in hospitals.** There are huge organizational governing bodies for Medication Safety Management, Donor Milk treatment and storage policies, enteral nutrition safety, formula preparation and mixing standards, infection control, and the list goes on.

Why does no one "own this?" Who **would** own this? Who **should** own this? If there is no governing body doing research, making recommendations, lobbying for change how will anything happen? It is up to us as clinical and administrative leaders who are invested in improving infant feeding safety to lead the charge.

Probiotic Research In Neonates With Congenital Gastrointestinal Surgical Conditions – Now Is The Time

Shripada C Rao[1,2,*] and Sanjay K Patole[2,3]

The major congenital gastrointestinal surgical conditions (CGISC) include oesophageal atresia, gastroschisis, exomphalos, malrotation and volvulus, duodenal atresia, intestinal atresia, meconium ileus, hypoplastic colon, meconium peritonitis, intestinal stenosis, congenital short bowel syndrome, Hirschsprung disease (HD), anorectal malformations and others. In addition to surgical repair, strategies for managing such conditions include early commencement of enteral feeds, standardization of feeding advancement, strict hand hygiene and aseptic precautions for indwelling catheters (Graham, 2010; Lauriti et al, 2014; Savoie et al, 2016; Dama et al, 2017). Despite such best practices and advances in surgical techniques, morbidities including feed intolerance, healthcare-associated infections, cholestatic jaundice, growth failure and neurodevelopmental disabilities continue to impose significant health burden on this cohort (Willis et al, 2010; Bishay et al, 2012; Wang et al, 2014; Dwyer et al, 2016; Hong et al, 2018). Additional strategies are hence required to improve their outcomes.

Gut dysbiosis in infants with CGISC

Neonatal gut microbiota develops rapidly after birth and achieves an adult-like composition and stability by 2-3 years of age (Arrieta et al, 2014). The evolution of gut microbiome is affected in infants with CGISC admitted in intensive care units (ICUs). These infants receive parenteral nutrition (PN), get exposed to multiple courses of antibiotics, do not receive early enteral feeding and optimal maternal skin to skin contact. Decontamination of the skin for surgery, exposure to gastric acid suppressants, breakdown of natural barriers due to invasive procedures and indwelling tubes and catheters, colonization of the ICU room surfaces and hands of the healthcare providers also contribute to the risk of gut dysbiosis in infants with CGISC (Donnell et al, 2002; van Saene et al, 2003; Hussey et al, 2011; Fouhy et al, 2012; Ralls et al, 2016; Rogers et al, 2016; Kitsios et al, 2017).

(i) **PN and gut dysbiosis:** The role of PN in gut dysbiosis deserves attention as it is often the main/only source of nutrition in infants with CGISC. Lavallee et al (2017) randomized neonatal piglets to receive total parenteral nutrition (TPN) or sow feeds (SF) for 14 days. Ileal segments and mucosal scrapings were used to assess the microbiota composition by 16S rRNA gene sequencing. Significant dysbiosis was noted in the TPN group, especially in those which received soy-based lipids. In another study, using a mouse model, Ralls et al (2016) reported permeation of TPN-derived nutrients into the gut lumen, where they were preferentially utilized by Enterobacteriaceae, which then flourished.

(ii) **Antibiotics and gut dysbiosis:** Fouhy et al (2012) compared the gut microbiota of nine newborn infants treated with parenteral ampicillin and gentamicin, with that of nine matched healthy infants. Gut microbiota of the antibiotic-treated infants showed significantly higher proportions of Proteobacteria and lower proportions of Actinobacteria and the associated genus Bifidobacterium, as well as the genus Lactobacillus compared with the untreated controls 4 weeks after the cessation of treatment. Even by week 8, Proteobacteria levels remained significantly higher in the treated infants (Fouhy et al, 2012). Increased abundance of Proteobacteria is a concern because it is considered as a potential diagnostic signature of dysbiosis and risk of disease (Shin et al, 2015).

(iii) **The ICU ecosystem and gut dysbiosis:** In a study in adult ICU patients, McDonald et al (2016) showed evidence of extreme dysbiosis. The phylogenetic diversity at discharge was significantly lower than at admission. Faecal samples tended to have a lower relative abundance of Firmicutes and Bacteroidetes and an increased relative abundance of Proteobacteria and well-recognized pathogens such as Enterobacter and Staphylococcus (McDonald et al, 2016). In a study in paediatric ICUs, Rogers et al (2016) reported taxonomic alterations in the gut microbiota. These included enrichments of gut pathogens such as Enterococcus and Staphylococcus at multiple body sites and depletion of commensals such as Faecalibacterium and Ruminococcus from stool samples. Alpha and beta diversity were unstable over time (Rogers et al, 2016).

Studies have shown an association between gut dysbiosis and morbidities such as hospital-acquired infections in neonates with surgical conditions (Donnell et al, 2002; van Saene et al, 2003) and Hirschsprung-associated enterocolitis (HAEC) (Li et al, 2016).

[1]Neonatal Intensive Care Unit, Perth Children's Hospital, Hospital Avenue, Nedlands, WA 6009, Australia. [2]Centre for Neonatal Research and Education, University of Western Australia, Perth, WA, Australia. [3]Neonatal Directorate, King Edward Memorial Hospital for Women, Perth, WA, Australia.

Probiotics for CGISC

Given that gut dysbiosis occurs and is associated with morbidities in infants with CGISC, optimization of gut microbiota by probiotics is a potentially beneficial strategy to improve their outcomes.

Probiotics are defined as live microorganisms that when administered in adequate amounts confer health benefits on people with specific illnesses (Hill et al, 2014). Probiotics inhibit gut colonization with pathogenic bacteria (Sassone-Corsi and Raffatellu, 2015), enhance gut barrier function (Bron et al, 2017), facilitate colonization with healthy commensals (Garrido et al, 2012), protect from enteropathogenic infection through production of acetate (Fukuda et al, 2011), reduce antimicrobial resistance (Taft et al, 2018), enhance innate immunity (Giorgetti et al, 2015) and increase maturation of the enteric nervous system and promote gut peristalsis (Hyland and Cryan, 2016; De Vadder et al, 2018). Through these mechanisms, probiotics have the potential to decrease the risk of sepsis, improve feed tolerance and minimize parenteral nutrition-associated cholestasis in infants with CGISC.

(i) **Evidence from studies in adult patients:** A recent meta-analysis of 20 RCTs (N = 1374) concluded that probiotic/symbiotic supplementation decreases the risk of surgical site and urinary tract infections in patients undergoing abdominal surgery (Lytvyn et al, 2016). Another meta-analysis that included 28 RCTs (n = 2511) involving adult patients undergoing gastrointestinal surgery came to similar conclusions (Yang et al, 2017). The durations of hospital stay and antibiotic therapy were shorter in the probiotics/symbiotic group vs controls (Yang et al, 2017). The need for caution in interpreting the results was emphasized considering the high risk of bias in included studies (Lytvyn et al, 2016; Yang et al, 2017).

(ii) **Evidence from studies in paediatric patients:** In a RCT, 30 children (<15 years) with various surgical (majority gastrointestinal) conditions were supplemented with probiotic Bifidobacterium breve BBG-01 or placebo daily from 7 days before the surgery until discharge. Probiotic supplementation was safe. It improved the gut flora, increased the concentration of faecal acetic acid and decreased the risk of septicaemia (Okazaki et al, 2016). A recent meta-analysis that included 198 infants with HD (two RCTs, three observational studies) reported that the incidence of HAEC 22.6% in the probiotic group vs 30.5% in the controls, but the difference was not statistically significant (OR 0.72; 95% CI 0.37–1.39; P = 0.33; Nakamura et al, 2018). Majority of the infants in the included studies were outside the neonatal period.

(iii) **Evidence from studies in neonates:** A systematic review (Rao et al, 2018) that focussed on CGISC exclusively in the neonatal population found only two small RCTs (Murakami et al, 2016; Powell et al, 2016). The Powell et al (2016) RCT included 24 neonates with gastroschisis (Probiotics: 12, Placebo: 12). The probiotic supplement was administered for 6 weeks or until hospital discharge, whichever came first. Significant dysbiosis was noted in the study infants, and it was partially attenuated by administration of Bifidobacterium longum subsp. infantis (Powell et al, 2016). In the RCT by Murakami et al (2016), four surgical neonates (duodenal atresia, anorectal malformations) received probiotics, four received no probiotics. Bifidobacteriaceae was more abundant in neonates who had not received probiotics. It was concluded that surgical stress appeared to affect the intestinal microbiota considerably. The need for further RCTs in this area was emphasized.

Safety of probiotics

Evidence from over 35 RCTs with a total sample size of nearly 12 000 and observational studies with over 14 000 participants show that probiotics are beneficial and safe in preterm non-surgical infants (Olsen et al, 2016; Rao et al, 2016; Sawh et al, 2016; Dermyshi et al, 2017). Even a large RCT that did not show benefits of probiotic supplementation acknowledged that short-term safety of probiotics was good in preterm infants (Costeloe et al, 2016). Recent meta-analyses have shown that probiotics do not increase or decrease the risk of intraventricular haemorrhage, chronic lung disease, retinopathy of prematurity and neurodevelopmental outcomes in preterm non-surgical infants (Cavallaro et al, 2017; Villamor-Martinez et al, 2017; Upadhyay et al, 2018). These findings provide reassurance regarding medium-term safety of probiotics in preterm infants. However, there are few case reports of sepsis due to probiotic organisms (Ohishi et al, 2010; Vallabhaneni et al, 2015; Brecht et al, 2016). Hence, constant vigilance and quality assurance of the product while conducting RCTs of probiotic supplementation in infants with CGISC are warranted.

Ongoing RCTs of probiotics in infants with CGISC

To our knowledge, currently, there are two ongoing RCTs evaluating the role of probiotics in this area. One trial is being conducted in Calgary (Canada) and aims to recruit 88 infants born between 23 and 42 weeks of gestation who require gastrointestinal surgery (Mugarab-Samedi et al, 2017). The probiotic supplement is FloraBabyTM (Renew Life Canada, Oakville, ON, Canada). Each sachet (1 g) will have 4 billion colony-forming units (CFU) of probiotics, consisting of Bifidobacterium breve (HA-129), Lactobacillus rhamnosus (HA111), Bifidobacterium bifidum (HA-132), Bifidobacterium longum subsp. infantis (HA-116) and Bifidobacterium longum subsp. longum (HA-135). Placebo is maltodextrin. The primary outcome of interest is length of hospital stay. Stool microbial analysis using culture independent 16S rRNA studies will be undertaken.

The other study (ours) is being conducted in Western Australia (Rao et al, 2017). Sixty infants (≥35 weeks' gestation) with major CGISC will be recruited. The probiotic group will receive 3×10^9 CFU/day (ie 3 billion organisms) in 1.5 ml of the expressed breast milk or sterile water, given as a single daily dose via the orogastric/nasogastric feeding tube or orally. The probiotic sachet (Morinaga Industries, Tokyo, Japan) will contain a mixture of three strains (B. breve M-16V, B. longum subsp. infantis M-63 and B. longum subsp. longum BB536 (1×10^9 CFU of each strain per 1 g sachet). Placebo is maltodextrin. Supplementation will be commenced as soon as possible after admission once the baseline stool samples are collected and will be continued until discharge. Primary outcome will be gut microbiota (using 16 s ribosomal RNA Pyrosequencing studies for phylogenic profiling) on stool samples. Secondary outcomes will be stool short-chain fatty acids and relevant clinical outcomes.

Conclusions

In summary, probiotic supplementation has the potential to minimize gut dysbiosis and improve clinical outcomes of neonates with CGISC. Though small, the completed and ongoing RCTs will provide important data and confidence to embark on adequately powered large RCTs in this exciting area.

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The Effect of Enteral Bolus Feeding on Regional Intestinal Oxygen Saturation in Preterm Infants is Age-Dependent: A Longitudinal Observational Study

Sara J Kuik[1*], Anne G J F van Zoonen[2], Arend F Bos[1], Koenraad N J A Van Braeckel[1], Jan B F Hulscher[2] and Elisabeth M W Kooi[1]

Abstract

Background: The factors that determine the effect of enteral feeding on intestinal perfusion after preterm birth remain largely unknown. We aimed to determine the effect of enteral feeding on intestinal oxygen saturation ($r_{int}SO_2$) in preterm infants and evaluated whether this effect depended on postnatal age (PNA), postmenstrual age (PMA), and/or feeding volumes. We also evaluated whether changes in postprandial $r_{int}SO_2$ affected cerebral oxygen saturation (r_cSO_2).

Methods: In a longitudinal observational pilot study using near-infrared spectroscopy we measured $r_{int}SO_2$ and r_cSO_2 continuously for two hours on postnatal Days 2 to 5, 8, 15, 22, 29, and 36. We compared preprandial with postprandial values over time using multilevel analyses. To assess the effect of PNA, PMA, and feeding volumes, we performed Wilcoxon signed-rank tests or logistic regression analyses. To evaluate the effect on r_cSO_2, we also used logistic regression analyses.

Results: We included 29 infants: median (range) gestational age 28.1 weeks (25.1-30.7) and birth weight 1025 g (580-1495). On Day 5, $r_{int}SO_2$ values decreased postprandially: mean (SE) 44% (10) versus 35% (7), P = .01. On Day 29, $r_{int}SO_2$ values increased: 44% (11) versus 54% (7), P = .01. Infants with a PMA ≥ 32 weeks showed a $r_{int}SO_2$ increase after feeding (37% versus 51%, P = .04) whereas infants with a PMA < 32 weeks did not. Feeding volumes were associated with an increased postprandial $r_{int}SO_2$ (per 10 mL/kg: OR 1.63, 95% CI, 1.02-2.59). We did not find an effect on r_cSO_2 when $r_{int}SO_2$ increased postprandially.

Conclusions: Our study suggests that postprandial $r_{int}SO_2$ increases in preterm infants only from the fifth week after birth, particularly at PMA ≥ 32 weeks when greater volumes of enteral feeding are tolerated. We speculate that at young gestational and postmenstrual ages preterm infants are still unable to increase intestinal oxygen saturation after feeding, which might be essential to meet metabolic demands.

Background

Introducing preterm infants to enteral feeding is challenging. Gastrointestinal (GI) motility of preterm infants is limited causing delay in gastric emptying and intestinal transit. This in turn could easily result in intolerance to feeding [1]. Enteral feeding has beneficial effects on the structural and functional development of the GI tract [1, 2]. The passage of enteral feeds leads to an increased metabolic demand on the small intestine. This results in increased intestinal perfusion from the superior mesenteric artery (SMA) known as postprandial hyperaemia [3, 4]. If this increased metabolic demand after enteral feeding cannot be met, feeding intolerance (FI) may occur, resulting in delayed full enteral feeding (FEF) and possibly even necrotizing enterocolitis (NEC) [5-8]. Furthermore, as preterm infants are at risk of impaired cerebrovascular autoregulation, postprandial redistribution of blood in favour of the intestines may result in cerebral underperfusion [9-11].

Near-infrared spectroscopy (NIRS) is a non-invasive method to assess end-organ perfusion in preterm infants [8, 12-14]. It allows us to measure regional tissue oxygen saturation (rSO_2) continuously [12-14]. From this measure fractional tissue oxygen extraction (FTOE) can be calculated, which reflects the balance between oxygen delivery and consumption [12-14].

Recent studies on NIRS or Doppler flow measurements of the SMA reported that healthy preterm infants, who tolerate enteral feeding of at least 100 mL/kg/day, demonstrate increased intestinal postprandial perfusion while cerebral perfusion remains stable [2, 15-17]. Nevertheless, little is known about whether this capability of the premature intestine to increase its perfusion after feeding is dependent on postnatal age (PNA), postmenstrual age (PMA), and/or feeding volumes. In addition, it remains unclear if cerebral perfusion also remains stable when postprandial redistribution of blood in favour of the intestines occurs soon after birth or in younger infants. Furthermore, studies that evaluated whether the presence or absence of postprandial intestinal hyperaemia is associated with the development of FI or with the development of NEC, are limited. Therefore our aim was to determine the effect of enteral bolus feeding on intestinal oxygen saturation ($r_{int}SO_2$) and extraction in preterm infants during the first five weeks after birth, and to evaluate whether this effect depended on PNA, PMA, and/or feeding volumes. Furthermore, we explored whether the cerebral oxygen saturation (r_cSO_2) and extraction changed when postprandial $r_{int}SO_2$ increased after enteral feeding.

Methods

Participants

For this prospective, longitudinal, observational, exploratory

[1]University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Division of Neonatology, Groningen, the Netherlands.
[2]University of Groningen, University Medical Center Groningen, Department of Surgery, Division of Pediatric Surgery, Groningen, the Netherlands.

study we derived patients from a larger observational cohort study at our tertiary referral neonatal intensive care unit (NICU) that aimed to identify prognostic markers for the development of NEC in high-risk neonates (CALIFORNIA-Trial, Dutch Trial Registry NTR4153) [18, 19]. For this trial, all infants who were at high risk of developing NEC, who were born between October 2012 and February 2014, and had been admitted to our NICU were eligible for inclusion. High-risk infants were defined as infants with a gestational age (GA) of less than 30 weeks or a birth weight (BW) of less than 1000 g, or a GA of less than 32 weeks and a BW below 1200 g, or preterm-born infants who had been exposed to indomethacin antenatally [20]. Exclusion criteria were congenital abdominal malformations or large chromosomal defects. For this pilot sub-study, which was part of a new scientific project, we started with precisely recording the feeding times from August 2013 onwards and included all preterm infants born between August 2013 and January 2014 and who had been admitted to our NICU. All infants were included after their parents had given written informed consent within 72 h after birth. The study was approved by the ethical review board of University Medical Center Groningen.

Feeding data

All infants received enteral feeding through nasogastric tubes. Feedings consisted of preterm formula, mother's own milk, donor mother's milk, or a combination. Infants who weighed less than 1200 g received enteral bolus feeding every two hours for 10 to 15 min by tube and open syringe using gravity. Infants who weighed more than 1200 g were fed once every three hours. As feeding volumes are relatively larger in case of bolus feeding once every three hours than once every two hours, we recorded feeding volumes in mL/kg/day but also in mL/kg during the NIRS measurement. All infants received 10 to 20 mL/kg on the first day after birth. Subsequently, feeding volumes were increased daily by 20 mL/kg/day unless gastrointestinal problems, such as recurrent vomiting or gastric retentions exceeding 5 mL, occurred repeatedly.

The feeding times were recorded during the NIRS measurements. We recorded the time at which feeding commenced, that is the time the feeding bolus was connected to the feeding tube, and the time feeding ended, that is the time the feeding tube was empty, feeding volumes (expressed in mL), and the type of feeding received by the infant.

Gastrointestinal complications

We recorded whether infants developed FI, NEC or a spontaneous intestinal (SIP) perforation. FI was defined as > 50% decrease in ml/kg/day of enteral feeding or withdrawal of enteral feeding because of abdominal distension, vomiting, abundant gastric retentions, bilious or bloody gastric retentions, or bloody stools.

Clinical characteristics

Prospectively, we collected data on GA, BW, PMA, PNA, sex, Apgar scores, SNAPPE-II score as measure for severity of illness [21], respiratory support, PCO_2, pH, haemoglobin, systolic, diastolic, and mean arterial blood pressure, the need for fluid resuscitation or inotropic support, the presence of a hemodynamically significant patent ductus arteriosus (PDA), and the presence of cerebral pathologies on cerebral ultrasound.

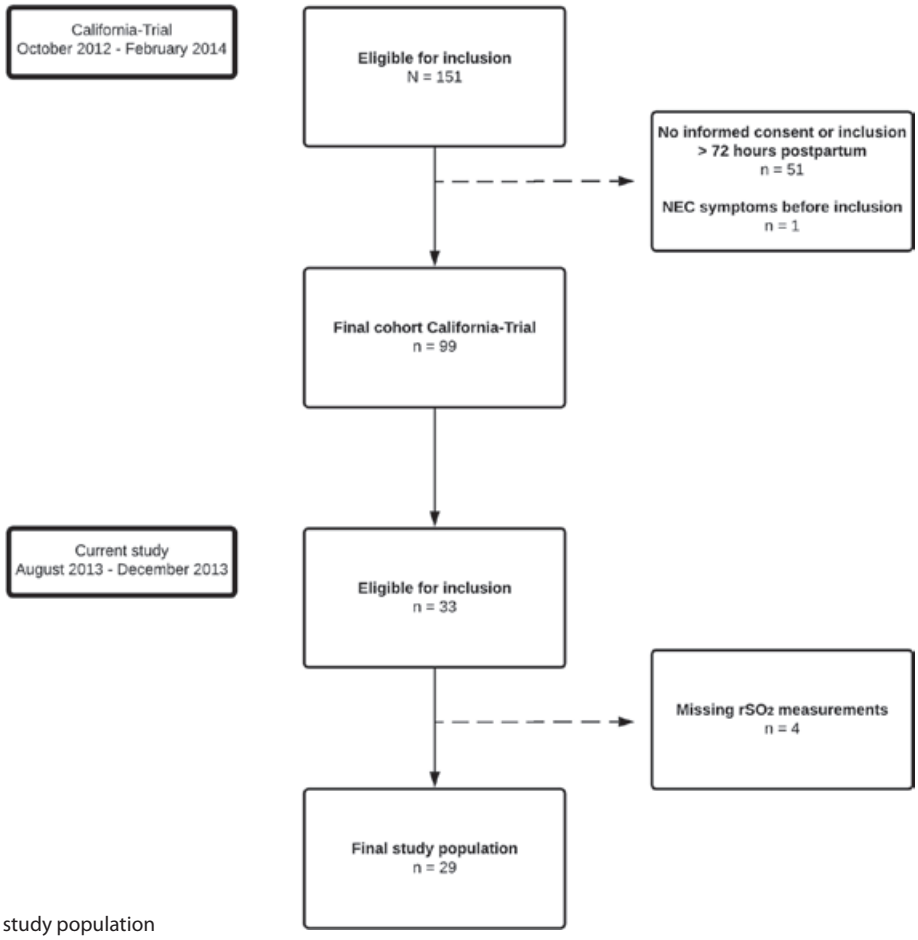

Fig. 1 Flow diagram of the study population

Near-infrared spectroscopy

We used the INVOS 5100C near-infrared spectrometer in combination with neonatal SomaSensors (Medtronic, Dublin, Ireland) to measure $r_{int}SO_2$ and r_cSO_2. We used Mepitel® film (Mölnlycke, Sweden), which does not adversely affect INVOS integrity or validity [22], to keep the sensor in place and as a skin barrier below each sensor. To measure $r_{int}SO_2$ we placed the sensor infraumbilically on the central abdomen. To measure r_cSO_2 we placed the sensor on the left or right frontoparietal side of the head. Intestinal and cerebral rSO_2 were measured for two uninterrupted hours, starting at 5 min prior to feeding, during postnatal Days 2 to 5, 8, 15, 22, 29, and 36. The study ended prior to Day 36 if an infant developed NEC Bell Stage ≥2, died, or was discharged from the NICU. We removed artefacts from the rSO_2 measurements. Artefacts were defined as instances recorded as sensor displacement, or a sudden major non-physiologic increase or decrease of the rSO_2 values within seconds, which suggests an incorrect measurement. We measured transcutaneous arterial oxygen saturation (SpO_2) simultaneously with the rSO_2 measurements using Nellcor (Medtronic) sensors. Next, we calculated intestinal and cerebral FTOE with the following formula: $(SpO_2\text{-}rSO_2)/SpO_2$. The FTOE reflects the balance between oxygen delivery to the tissue measured and oxygen consumption of the tissue measured, and depends less on changes in arterial oxygen saturation [10].

Statistical analyses and sample size

For statistical analyses we used SPSS 23.0 (IBM Corp., Armonk, NY, USA). We described the patient characteristics in terms of median (range) values. First, after confirming normal distribution of the data, we calculated the mean and standard error of the mean (SE) of all NIRS measurements at three points in time on postnatal Days 2 to 5, 8, 15, 22, 29, and 36, viz. 5 min prior to feeding and 10 to 30 min and 30 to 60 min after feeding had commenced. SE was preferred over standard deviation, given the comparison of means and given the small sample size, which may hamper accurate estimation of the means [23, 24]. Next, we built a multilevel model for each dependent variable using the statistical program MLwiN 2.15 (University of Bristol, Bristol, UK) [25]. Given the presence of missing data, an advantage of multilevel analysis is that this analysis calculates weighted means and their standard errors, which takes the number of data points per infant into account, thus allowing infants with more data points to weigh more into the estimated mean than infants with less data points. Four models, one for each dependent variable ($r_{int}SO_2$, r_cSO_2, intFTOE, and cFTOE) were specified with measurements (Level 1) nested within subjects (Level 2). Thus, the dependency between measurements was taken into consideration in which the intercept represented the baseline measurement (before feeding) on Day 2. To compare preprandial measurements with measurements 10 to 30 and 30 to 60 min postprandially, each model consisted of 27 terms (9 days multiplied by the three points in time; that is each term is defined as one measurement of one day). A t test was used to test for differences between an estimated mean and the intercept [26]. We tested the contrast of the sum of parameters from which each estimate is derived using a chi-square test with one degree of freedom to test for differences between two estimated means.

Second, to evaluate whether the effect of enteral bolus feeding on the $r_{int}SO_2$ depended on PMA, we clustered the measurements into different groups, that is PMA < or ≥ 30 weeks and < or ≥ 32 weeks and performed a Wilcoxon signed rank test between preprandial and postprandial $r_{int}SO_2$ values. Next, to determine whether feeding volumes were associated with the effect of enteral feeding on $r_{int}SO_2$, we used a univariate logistics regression analysis between postprandial $r_{int}SO_2$ values (categorized into increase or no increase) and the amount of the bolus enteral feeding per 10 mL/kg.

Thereafter, to explore whether a postprandial $r_{int}SO_2$ increase was associated with a decreased postprandial r_cSO_2, we performed a logistic regression analysis between categorized data; that is increase or no increase of the $r_{int}SO_2$ versus decrease or no decrease of the r_cSO_2. Finally, we performed a subanalysis between infants who did and did not develop any GI complications. Infants were categorized into four groups; Uncomplicated, FI, NEC, and SIP. As two out of the three NEC infants developed NEC within 14 days, we clustered the data from the first two postnatal weeks and calculated delta's between baseline $r_{int}SO_2$ and postprandial $r_{int}SO_2$ values, and performed a Mann Whitney U between delta's of the infants with and without a GI complication. For this subanalysis, we used a non-parametric test as the delta's in this small sample size were not normally distributed and therefore presented these data in medians [IQRs].

Throughout the analyses a P value < .05 was considered statistically significant. We chose not to correct for multiple testing in this explorative study.

Results

Patient characteristics

We included 29 patients out of 33 eligible patients (Fig. 1). We had to exclude four infants because of missing rSO_2 data. The 29 remaining infants had a median GA of 28.1 weeks (range 25.1-30.7) and a median BW of 1025 g (range 580-1495). Table 1 provides an overview of the patient characteristics. Three infants died during the study period after a median of 21 days (range 16-25) after birth: one infant died of NEC, one of multi-organ failure as a result of sepsis, and one infant died of progressive respiratory failure. Three infants developed NEC Bell's Stage ≥2 on postnatal Days 7, 10, and 30, respectively. Two infants developed a spontaneous intestinal perforation on postnatal Day 8 and Day 12. Thirteen patients were discharged from the NICU prior to the 36th day (from Day 15 onward). In 16 patients we were unable to measure intestinal NIRS during the first two to eight days after birth because of the placement of umbilical catheters taped to the infraumbilical skin or as a result of a lack of space on the infants' abdomens.

The effect of feeding on intestinal oxygenation in relation to postnatal age

On Day 5, mean postprandial $r_{int}SO_2$ values were lower than mean preprandial values: 10 to 30 min after feeding $r_{int}SO_2$ was 38% (SE 7) versus 44% (SE 10) before feeding, just failing to reach significance (n = 12, P = .07), while 30 to 60 min after feeding the decrease was significant (35%, SE 7, versus 44%, SE 10, n = 12, P = .01). On Day 29 (median postmenstrual age: 31.7 weeks, range 29.3-34.7), mean postprandial $r_{int}SO_2$ values 10 to 30 min after feeding increased with respect to preprandial values ($r_{int}SO_2$ 54%, SE 7, versus 44%, SE 11, n = 10, P = .01). The intFTOE did not change concomitantly. We provide a complete overview of the results in Table 2 and Fig. 2.

The effect of feeding on $r_{int}SO_2$ in relation to postmenstrual age

We found that infants with a PMA ≥ 32 weeks showed a

Table 1 Patient characteristics during the study period

Study population	*n* = 29
Boys/Girls	16/13 (65%/45%)
Gestational age, weeks	28 + 1 (25 + 1–30 + 5)
Birth weight, g	1025 (580–1495)
Sets of twins	4 (14%)
Small-for-gestational-age (*P* < 10)	6 (21%)
Head circumference on day of birth, centimetres	25.0 (22.5–29.0)
Apgar score at 5 min	7 (2–9)
SNAPPE-II score	28 (0–77)
Intestinal pathologies	
Necrotizing enterocolitis/spontaneous intestinal perforation	4 (14%)
Sepsis (including suspected sepsis)	22 (76%)
Circulatory failure	
Fluid resuscitation	7 (24%)
Inotropic treatment	2 (7%)
Respiratory support[a]	
Mechanical ventilation	16 (55%)
Continuous positive airway pressure	27 (93%)
High flow	7 (24%)
Low flow or no support	15 (52%)
Cerebral lesions	
Germinal matrix haemorrhage-intraventricular haemorrhage	
Grade I	6 (21%)
Grade II	2 (7%)
Transient periventricular echodensities	10 (34%)
Periventricular leukomalacia	13 (45%)
Patent ductus arteriosus	
Expectative policy	7 (24%)
Ibuprofen treatment	6 (21%)
Surgical clip	3 (10%)
Hyperbilirubinemia	23 (79%)
Anaemia	19 (66%)
Hemoglobin (mmol/L)	
Day 2	9.1 (7.6–11.6)
Day 3	9.0 (6.5–11.6)
Day 4	8.6 (6.5–11.9)
Day 5	8.4 (6.8–11.9)
Day 8	8.5 (6.9–10.6)
Day 15	8.2 (6.2–9.7)
Day 22	8.0 (5.7–8.4)
Day 29	7.8 (6.2–9.5)
Day 36	8.3 (6.4–9.8)
Enteral feeding[a]	
Mother's milk	24 (83%)
Preterm formula	20 (69%)
Donor mother's milk	10 (34%)
Infusion rate bolus feeding (mL/min)	3.4 (0.1–60.0)

Abbreviations: SD, standard deviation. SNAPPE-II, Score for Neonatal Acute Physiology - Perinatal Extension II. The data are expressed as median (range) or as numbers (percentages) unless otherwise specified. [a]The numbers exceed totals, because a single infant could have several respiratory supports and several types of enteral feeding during the first 36 days after birth

significant postprandial increase of the $r_{int}SO_2$ 10 to 30 min after feeding (37% versus 51%, P = .04, n = 10, 13 measurements) and a non-significant increase 30 to 60 min after feeding (37% versus 44%, P = .06, n = 10, 13 measurements). All data are presented in Fig. 3.

The effect of enteral bolus feeding on $r_{int}SO_2$ in relation to feeding volumes

We found a significant association between feeding volumes (mL/kg) and the change in $r_{int}SO_2$ 10 to 30 min after feeding. For every 10 mL/kg more enteral feeding per bolus 10 to 30 min after feeding, the odds score for an increasing postprandial $r_{int}SO_2$ was 1.6 times higher (95% CI, 1.02-2.59, P = .04). Feeding volumes were not significantly associated with the change in $r_{int}SO_2$ 30 to 60 min after feeding. Table 3 provides an overview of enteral feeding volumes.

The effect of a changing intestinal oxygenation after feeding on cerebral oxygenation

Clustering all feeds observed, for all instances that the postprandial $r_{int}SO_2$ increased, the median postprandial increase was 7% (range 1-41, n = 21, 42 measurements) 10 to 30 min and 11% (range 1-41, n = 22, 40 measurements) 30 to 60 min after feeding, respectively. For all instances that the postprandial r_cSO_2 decreased, median postprandial decrease was –5% (range –22 to –1, n = 29, 77 measurements) 10 to 30 min and –4% (range –31 to –1, n = 29, 82 measurements) 30 to 60 min after feeding, respectively. We did not find an association between an increasing postprandial $r_{int}SO_2$ and a decreasing postprandial r_cSO_2. We did, however, find that the absence of an increasing postprandial $r_{int}SO_2$ was significantly associated with a 3.6 times higher odds ratio for a decreasing r_cSO_2 10 to 30 min (95% CI, 1.5-8.9, P = <.01) and a 3.0 times higher odds ratio for a decreasing r_cSO_2 30 to 60 min (95% CI, 1.2-7.3, P = .02) after feeding. Preprandial and postprandial r_cSO_2 (and cFTOE) values are presented in Table 2.

Infants with and without the development of gastrointestinal complications

Seven infants developed FI (24%), three infants developed NEC (10%), and two (7%) infants developed SIP.

We did not find a change in $r_{int}SO_2$ 10-30 min after feeding between infants who developed NEC and infants who did not develop a GI complication during the first two postnatal weeks. The infants who developed NEC, however, tended to have a decreasing $r_{int}SO_2$ 30-60 min after enteral feeding compared to infants without GI complications (-24% vs. 1%, P = .06) during the first two postnatal weeks (Fig. 4). There was no change in $r_{int}SO_2$ 10-30 min and 30-60 min after feeding between infants who developed FI and infant without GI complications, and between infants who developed SIP and infants without GI complications (Fig. 4).

Discussion

We demonstrated that in our group of preterm infants, born after approximately 28 weeks of gestation, a postprandial increase of intestinal oxygen saturation does occur, albeit at group level

Table 2 Preprandial compared to postprandial values of $r_{int}SO_2$, r_cSO_2, intFTOE, and cFTOE values on postnatal days

	M1 Mean (SE)	M2 Mean (SE)	M3 Mean (SE)	*P* value M1 vs. M2	*P* value M1 vs. M3
Day 2					
$r_{int}SO_2$ (%, *n* = 10)	40 (11)	38 (7)	40 (7)	.46	1.00
r_cSO_2 (%, *n* = 28)	77 (4)	77 (3)	78 (3)	.71	.43
intFTOE (*n* = 9)	0.48 (0.14)	0.57 (0.14)	0.47 (0.14)	.24	.85
cFTOE (*n* = 27)	0.13 (0.04)	0.14 (0.04)	0.13 (0.04)	.97	.90
Day 3					
$r_{int}SO_2$ (%, *n* = 7)	37 (11)	39 (7)	41 (7)	.58	.32
r_cSO_2 (%, *n* = 25)	75 (4)	76 (3)	76 (3)	.30	.37
intFTOE (*n* = 7)	0.58 (0.14)	0.48 (0.14)	0.51 (0.14)	.18	.31
cFTOE (n = 25)	0.17 (0.04)	0.17 (0.04)	0.16 (0.04)	.80	.46
Day 4					
$r_{int}SO_2$ (%, *n* = 11)	34 (10)	34 (7)	35 (7)	.91	.59
r_cSO_2 (%, n = 28)	73 (4)	72 (3)	73 (3)	.48	.83
intFTOE (*n* = 11)	0.65 (0.14)	0.59 (0.14)	0.57 (0.14)	.34	.19
cFTOE (*n* = 28)	0.18 (0.04)	0.20 (0.04)	0.17 (0.04)	.27	.67
Day 5					
$r_{int}SO_2$ (%, *n* = 12)	44 (10)	38 (7)	35 (7)	.07	.01*
r_cSO_2 (%, *n* = 27)	73 (4)	72 (3)	72 (3)	.32	.19
intFTOE (*n* = 12)	0.49(0.14)	0.58(0.14)	0.48 (0.14)	.16	.84
cFTOE (*n* = 27)	0.19 (0.04)	0.21 (0.04)	0.21 (0.04)	.26	.27
Day 8					
$r_{int}SO_2$ (%, *n* = 12)	39 (10)	38 (7)	35 (7)	.61	.21
r_cSO_2 (%, *n* = 25)	67 (4)	71 (3)	73 (3)	.01*	<.01*
intFTOE (*n* = 12)	0.59 (0.13)	0.56 (0.13)	0.62 (0.14)	.63	.66
cFTOE (n = 25)	0.25 (0.04)	0.22 (0.04)	0.20 (0.04)	.27	.03*
Day 15					
$r_{int}SO_2$ (%, *n* = 15)	34 (10)	39 (7)	38 (7)	.13	.15
r_cSO_2 (%, *n* = 19)	66 (4)	64 (3)	63 (3)	.22	.09
intFTOE (n = 15)	0.59 (0.13)	0.51 (0.13)	0.58 (0.13)	.17	.87
cFTOE (n = 19)	0.28 (0.05)	0.26 (0.04)	0.27 (0.04)	.33	.76
Day 22					
$r_{int}SO_2$ (%, n = 11)	48 (10)	47 (7)	45 (7)	.67	.35
r_cSO_2 (%, *n* = 14)	57 (4)	58 (3)	58 (3)	.46	.39
intFTOE (n = 11)	0.46 (0.14)	0.45 (0.14)	0.46 (0.14)	.93	.90
cFTOE (n = 14)	0.36 (0.05)	0.27 (0.05)	0.33 (0.04)	<.01*	.23
Day 29					
$r_{int}SO_2$ (%, n = 10)	44 (11)	54 (7)	50 (7)	.01*	.18
r_cSO_2 (%, n = 12)	62 (5)	63 (3)	62 (3)	.63	.87
intFTOE (n = 10)	0.43 (0.14)	0.40 (0.14)	0.45 (0.14)	.65	.78
cFTOE (n = 12)	0.26 (0.05)	0.27 (0.05)	0.28 (0.05)	.71	.42
Day 36					
$r_{int}SO_2$ (%, *n* = 8)	47 (11)	49 (7)	46 (7)	.56	.84
r_cSO_2 (%, n = 8)	65 (5)	65 (3)	66 (3)	.80	.52
intFTOE (n = 8)	0.40 (0.14)	0.37 (0.14)	0.50 (0.14)	.65	.21
cFTOE (n = 8)	0.26 (0.05)	0.26 (0.05)	0.23 (0.05)	.88	.37

Abbreviations: *M1* Measurement 1 (preprandial), *M2* Measurement 2 (10 to 30 min postprandial), *M3* Measurement 3 (30 to 60 min postprandial). The data are expressed as mean (standard errors of the mean) unless otherwise specified. * = *P* value < .05

only in the fifth week after birth or in infants of a relatively older corrected gestational age. Furthermore, we showed that not a postprandial increase of intestinal oxygenation, but rather the absence thereof, was associated with a higher risk of a decrease of the cerebral oxygen saturation.

Our results suggest that during the first four weeks after birth at group level, intestinal perfusion does not exceed any potential increased oxygen consumption after enteral feeding. In the fifth week after birth the PMA of the remaining infants was 31.7 weeks. We assume that during this period the postprandial

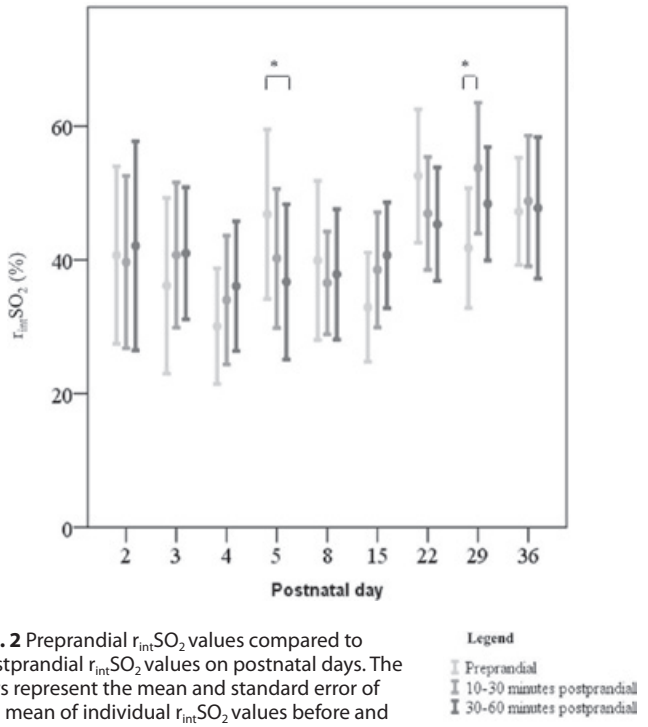

Fig. 2 Preprandial $r_{int}SO_2$ values compared to postprandial $r_{int}SO_2$ values on postnatal days. The bars represent the mean and standard error of the mean of individual $r_{int}SO_2$ values before and after enteral feeding. The mean $r_{int}SO_2$ is marked with a o within the bars. Statistically significant differences are marked with an asterisk: * < .05

effect of feeding on the intestinal rSO_2 can be explained by an increasing PMA rather than PNA, because we demonstrated that infants with a PMA ≥ 32 weeks have an increased postprandial $r_{int}SO_2$. In addition, by this time the remaining infants received relatively greater feeding volumes, which we demonstrated to be another important factor to elicit postprandial hyperaemia. Previous reports showed increased postprandial intestinal oxygen saturation using NIRS [2, 15, 16] or increased postprandial blood flow velocity of the SMA using Doppler measurements [3, 4], but these measurements were mainly done cross-sectionally, in fullterm and preterm infants with a corrected GA of at least 32 weeks, and were not assessed from birth onwards.

We offer several explanations for the fact that we did not find increased intestinal oxygen saturation after enteral bolus feeding during the first four weeks after birth and in the younger infants with a PMA < 32 weeks based on the principle that intestinal oxygenation consists of a balance between oxygen supply and consumption [15]. First, it may be that neither intestinal oxygen supply nor oxygen consumption changes in very preterm infants after enteral feeding because of intestinal immaturity on account of the fact that intestinal maturation is an ongoing process up to 33 to 34 weeks of gestation, and even beyond [27].

Besides intestinal immaturity, the low feeding volumes received during the first weeks after birth, especially in the youngest infants, may only result in a limited increase of intestinal metabolism and perfusion. Previous reports on animal models demonstrated a dose-dependent hyperaemic intestinal response after feeding [28, 29]. In addition, previous studies that reported increased intestinal perfusion after feeding were performed in preterm infants who tolerated feeding volumes of 100 mL/kg/day [2, 15-17]. We confirmed that indeed increased feeding volumes were associated with a higher chance of increasing intestinal saturation after feeding.

Another, but perhaps less likely explanation for not finding any change in intestinal oxygenation after feeding in the youngest infants, may come from a potentially perfect balance between oxygen supply and oxygen consumption. It may be that both increase equally after enteral feeding. One would, however, sooner expect such perfect harmony in the more mature infants.

Finally, several perinatal conditions may have influenced our findings. In comparison to populations reported on previously, our study population consisted of a relatively large proportion of infants who had a hemodynamically significant PDA. It has been demonstrated that preterm infants with large PDAs show a very slight increase of SMA blood flow velocities one hour after enteral bolus feeding compared to preterm infants without a PDA or a small or moderate PDA [30]. Therefore, in our study, the relative large proportion of infants with a PDA might have contributed to a lack of postprandial $r_{int}SO_2$ increase at group level. Additionally, other perinatal morbidities, (that is being born small for gestational age or anaemia, Table 1) may also have contributed to our results. Two recent studies demonstrated a lack of increase, or even a decrease, in postprandial $r_{int}SO_2$ in a group of anaemic preterm infants and in preterm infants who showed fetal signs of intrauterine growth restriction [31, 32]. Martini et al. showed that preterm infants with abnormal prenatal umbilical Doppler measurements lack any effect of the first enteral feeding on $r_{int}SO_2$ [29]. The results of these studies suggest that the intestinal response to enteral feeds is complex and that it is influenced by intestinal immaturity as well as intestinal condition and other perinatal factors [31, 32]. The hemoglobin levels in our study population decreased over time during the five weeks after birth, while we demonstrated that the $r_{int}SO_2$ increased after enteral feeding in the fifth week after birth. We therefore speculate that the maturing process of the intestine after birth and the greater feeding volumes have a larger contribution on the change in intestinal oxygen saturation after enteral feeding and attenuate the effect of the level of hemoglobin. Unfortunately, we were unable to perform subanalyses to address these issues on account of the size of our sample.

We did not observe an association between postprandially increased intestinal oxygen saturation and postprandially decreased cerebral oxygen saturation. On the contrary, we did find an association between a lack of a postprandial increase of the intestinal rSO_2 and the risk of a decreased cerebral rSO_2. We hypothesize that the infants with a lower PMA, who more often seemed to lack an adequate intestinal response, might have a less adequate cerebrovascular autoregulation and thus are at risk of compromised cerebral perfusion. A decrease of the cerebral oxygen saturation might indicate a decreased systemic circulation. One of the reasons for a decreased systemic circulation might be a lower cardiac output, but this might also be due to changes in blood pressure or redistribution of blood flow to other vital organs that temporarily have an increased metabolic demand. As the cerebral oxygen saturation is not a measure for cardiac output, assumptions concerning a decrease in cardiac output, or to what extent the cardiac output might have changed, cannot be made. Previously, stable cerebral oxygen saturation values were reported in studies that evaluated the effect of enteral feeding on rSO_2 in preterm infants [2, 16, 33, 34]. Combining these results with our results suggests that cerebral saturation is not compromised when intestinal perfusion increases after enteral bolus feeding, possibly on

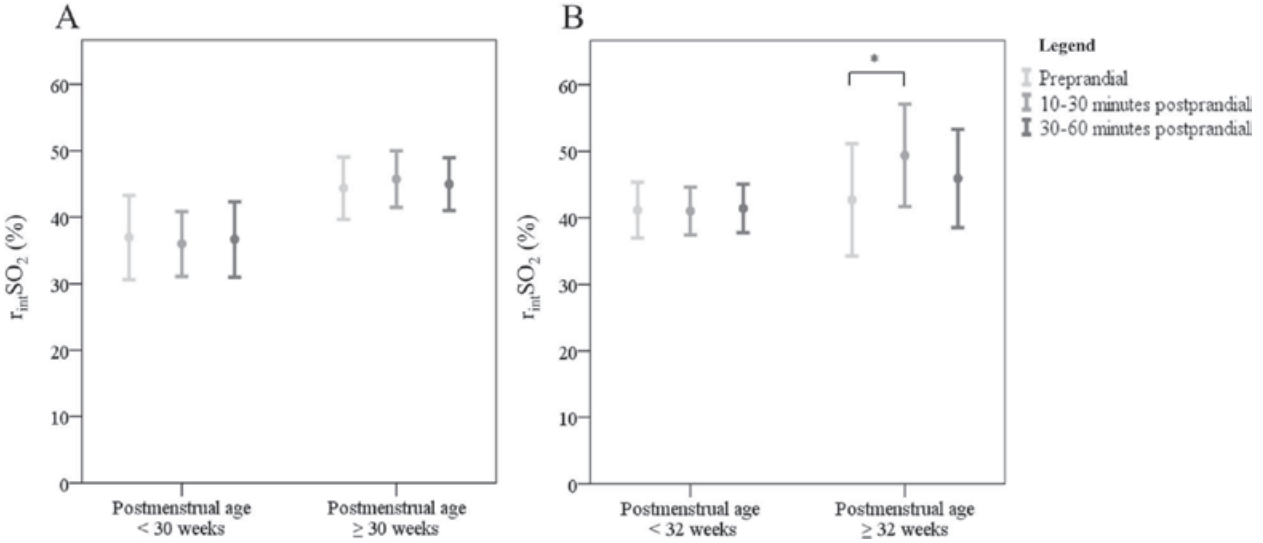

Fig. 3 Preprandial $r_{int}SO_2$ values compared to postprandial values between PMA groups The bars represent the mean and standard error of the mean of individual $r_{int}SO_2$ values before and after enteral feeding for the different PMA groups; PMA < or ≥ 30 weeks (**a**), PMA < or ≥ 32 weeks (**b**). The mean $r_{int}SO_2$ is marked with a o within the bars. Statistically significant differences are marked with an asterisk: * < .05

account of adequate cerebrovascular autoregulation, but that this may be age-dependent.

In our study, only a few infants developed NEC. The infants who subsequently developed NEC tended to have a decreasing intestinal oxygen saturation 30-60 min after bolus feeding during the first two postnatal weeks, whereas infants without GI complications, FI, and SIP did not. As a result of the very small number of infants, these results have to be carefully interpreted, and conclusions cannot be made based on these results, which require further investigation in a larger cohort.

An important strength of this exploratory study is the longitudinal design that created the opportunity to address the age-dependent component on the effect of enteral feeding on intestinal perfusion. Nevertheless, we also recognise several limitations to our study. The first limitation was the relative small population studied. Therefore we could not analyse the influence of comorbidities on intestinal perfusion after enteral feeding. Neither could we stratify the study cohort on the basis of feeding intervals or feeding type, nor could we perform multivariable regression analyses to test for possible confounding factors. Despite the fact that we performed several tests we chose not to correct for multiple testing, because we considered this observation to be exploratory and hypothesis generating. Another limitation concerns validity issues using NIRS to assess intestinal oxygenation. Movement of the gut, abdominal gasses, and stools could influence the signal because of absorption changes of the near-infrared light which is path-length dependent [6, 14, 31, 32, 35]. Additionally, standard limits of intestinal oxygen saturation are not yet established on account of the wide intervariability and intravariability of intestinal rSO_2 values [14, 16]. Finally, we clustered our data to determine whether the effect of enteral feeding on the intestinal rSO_2 depends on PMA.

Therefore the contribution of measurements per infant was unequally distributed and we might have underestimated or overestimated our results. Nevertheless, to our knowledge, this is the first longitudinal study demonstrating that enteral feeding only affects intestinal oxygen saturation after weeks, or when infants have reached 32 weeks PMA, and larger volumes of feeds.

Table 3 Enteral feeding volumes of all included infants per day and during NIRS measurement

Day	Feeding mL/kg/day	Feeding mL/kg/measurement
2 (n = 29)	20.8 (17.8–26.7)	2.1 (1.4–2.7)
3 (n = 29)	39.4 (27.9–43.3)	2.8 (2.3–4.1)
4 (n = 29)	56.3 (34.5–63.2)	4.4 (3.2–6.2)
5 (*n* = 29)	73.1 (44.5–80.9)	5.6 (3.9–7.8)
8 (n = 27)	101.2 (68.1–125.7)	8.9 (5.3–12.7)
15 (*n* = 23)	149.3 (88.8–152.3)	12.4 (8.7–13.3)
22 (*n* = 17)	150.1 (139.8–156.2)	14.0 (12.2–19.0)
29 (*n* = 12)	145.4 (127.7–153.2)	17.2 (11.9–18.6)
36 (*n* = 10)	149.5 (125.7–154.1)	18.4 (14.8–19.1)

The data are expressed as median (interquartile range)

Conclusions

Our results suggest that postprandial intestinal hyperaemia does only occur at group level from the fifth week after birth or in infants with relatively older corrected gestational ages receiving a greater amount of enteral feeding. In addition, we showed that postprandial intestinal hyperaemia is not associated with compromised cerebral perfusion. Our study provides more insight into the intestinal physiologic response to enteral feeding in preterm infants. A better understanding of this intestinal physiologic postprandial response might support clinicians in identifying infants at risk for the development of GI complications. This exploratory study, however, raises questions about when and why intestinal saturation does or does not increase after enteral bolus feeding in the early postnatal weeks of a preterm infant, and whether a decreasing intestinal perfusion after feeding may be associated with GI complications later on. Further study is required to address these issues. Moreover, larger studies addressing possible confounders on the intestinal haemodynamic response to enteral feeds, such as PDA and other perinatal morbidities, are needed.

Abbreviations

BW: Birth weight; cFTOE: cerebral fractional tissue oxygen

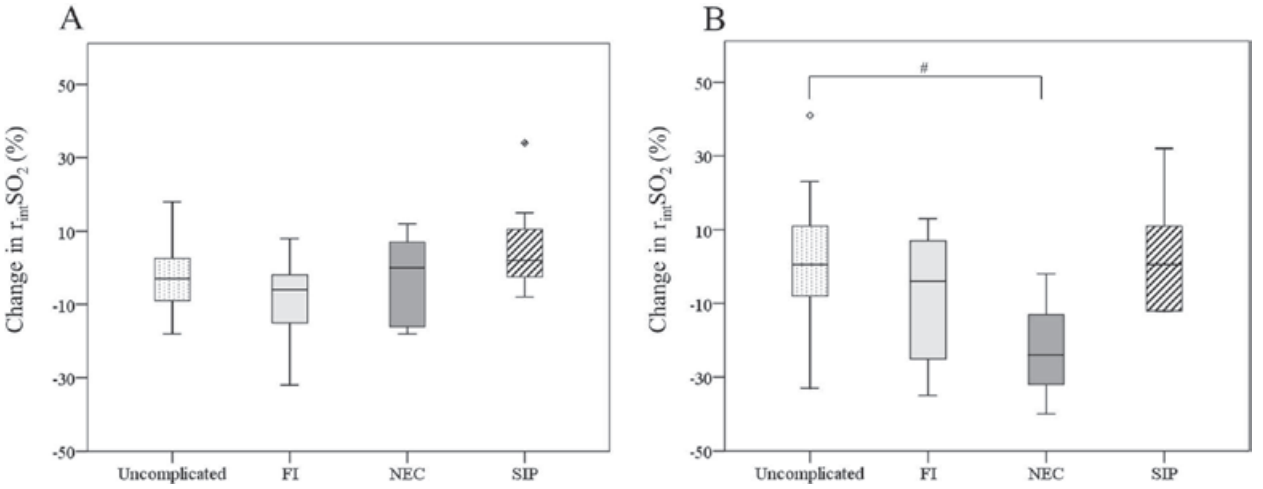

Fig. 4 Postprandial change in $r_{int}SO_2$ values in infants with and without abdominal complications The boxes represent the change in $r_{int}SO_2$ values of the clustered data from the first two postnatal weeks between the 25th and 75th centiles (interquartile range) between baseline and 10–30 min after feeding (**a**) and between baseline and 30–60 min after feeding (**b**) for infants without abdominal complications (uncomplicated), infants who developed feeding intolerance (FI), necrotizing enterocolitis (NEC), and a spontaneous intestinal perforation (SIP); the whiskers represent the range of the values with the exception of outliers. Outliers are represented by the circles and diamonds, defined as values between 1.5 interquartile range and 3 interquartile ranges from the end of a box. # < .10

extraction; CHD: Congenital heart disease; FEF: Full enteral feeding; FI: Feeding intolerance; FTOE: Fractional tissue oxygen extraction; GA: Gestational age; GI: Gastrointestinal; intFTOE: intestinal fractional tissue oxygen extraction; NEC: Necrotizing enterocolitis; NICU: Neonatal intensive care unit; NIRS: Near-infrared spectroscopy; PDA: Patent ductus arteriosus; PMA: Postmenstrual age; PNA: Postnatal age; r_cSO_2: Regional cerebral tissue oxygen saturation; $r_{int}SO_2$: Regional intestinal oxygen saturation; rSO_2: Regional tissue oxygen saturation; SE: Standard error of the mean; SMA: Superior mesenteric artery; SpO_2: Arterial oxygen saturation

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There is evidence-based guidance supporting the use of CPAP and NHF therapy in the NICU. A Cochrane Review published in 2016 by Wilkinson et al. included data from six post-extubation RCTs that compared the efficacy of CPAP and NHF for post-extubation support.

CPAP and NHF for post-extubation care

GESTATIONAL AGE (WEEKS): 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

< 28 weeks GA

CPAP first

as there is limited data and insufficient evidence to change clinical practice

Consider NHF once stable to:

- Reduce nasal trauma and head molding
- Facilitate developmental care

≥ 28 weeks GA

NHF first + Rescue CPAP

as data from large RCTs suggests that NHF is equivalent to CPAP, with less nasal trauma and no difference to adverse events

Consider CPAP as as "rescue" therapy if required

Willkinson et al. *Cochrane Database of Systematic Review.* 2016.

In infants ≥ 28 weeks gestational age, compared to CPAP, NHF is associated with:

- **NO DIFFERENCE** in rate of **treatment failure**
- **NO DIFFERENCE** in rate of **re-intubation**
- **SIGNIFICANT REDUCTION** in rate of **nasal trauma**
- **NO DIFFERENCE** in rates of **other adverse outcomes** such as death, pneumothorax, or bronchopulmonary dysplasia

Manley et al. 2013

N Engl J Med.

- 303 infants
- Single center in Australia
- Primary outcome: Treatment failure within 7 days

Collins et al. 2013

J Pediatr.

- 132 infants
- Single center in Australia
- Primary outcome: Treatment failure within 7 days

Liu et al. 2016

Chinese J Pediatr.

- 256 infants
- Single center in China
- Primary outcome: Treatment failure within 7 days

Campbell et al. 2006

J Perinatol.

- 40 infants
- Single center in USA
- Primary outcome: Need for intubation

Mostafa-Gharehbhagi et al. 2015

Zahedan J Res Med Sci

- 85 infants
- Single center in Iran
- Primary outcome: Treatment failure within 3 days

Yoder et al. 2013

Pediatrics

- 432 infants (226 in post-extubation arm)
- Centers: 4 in USA, 1 in China
- Primary outcome: Need for intubation within 72 hours

**NHF: Nasal High Flow, CPAP: Continuous Positive Airway Pressure, NICU: Neonatal Intensive Care Unit; RCT: Randomized Controlled Trial*

Wilkinson et al. *Cochrane Database Sys Rev.* 2016. Manley et al. *NEJM.* 2013. Yoder et al. *Pediatrics.* 2013. Collins et al. *J Pediatr.* 2013. Liu et al. *Chinese J Peds.* 2016. Campbell et al. *J Perinatol.* 2006. Mostafa-Gharehbhagi et al. *Zahedan J Res Med Sci.* 2015.

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